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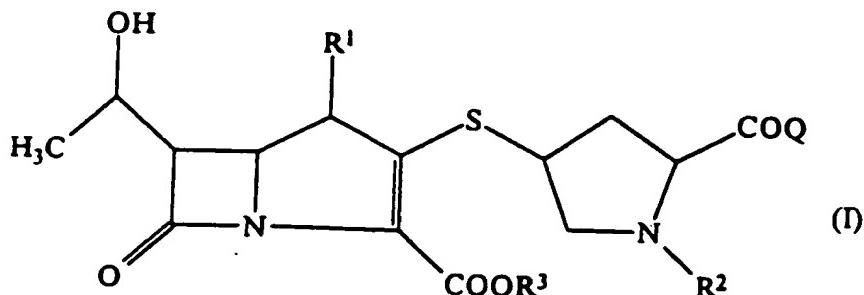
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(54) Antimicrobial carbapenem derivatives, their preparation and their therapeutic use.

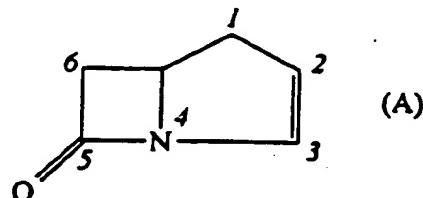
(57) Compounds of formula (I) :



(in which R¹ is hydrogen or methyl, R² is hydrogen, optionally substituted aliphatic hydrocarbon or acylimid yl, R³ is hydrogen or an ester group, and Q is an optionally quaternized nitrogen-containing group) are useful antibiotics which are resistant to dehydropeptidase I, and are thus useful for the treatment of many microbial infections.

The present invention relates to a series of new carbapenem derivatives which have excellent antimicrobial activities and which, by virtue of their enhanced resistance to inactivation by dehydropeptidase I, have improved value in the therapy and prophylaxis of infectious diseases. The invention also provides methods of preparing these compounds, as well as methods and compositions using them.

The carbapenem compounds are a well known series of compounds, related to the penicillins, which have been used or have been proposed for use as antibiotics. They have in common a basic structure which may be represented by the formula (A):



In this formula, we have indicated the numbering of those positions of importance to the carbapenem compounds, using the numbering scheme commonly used in the art and as employed in the nomenclature of the compounds of the present invention. In accordance with the recommendations of the International Union of Pure and Applied Chemistry (IUPAC), Commission on Nomenclature of Organic Chemistry, the compounds referred to herein are named semi-systematically, using the above carbapenem structure as the parent name.

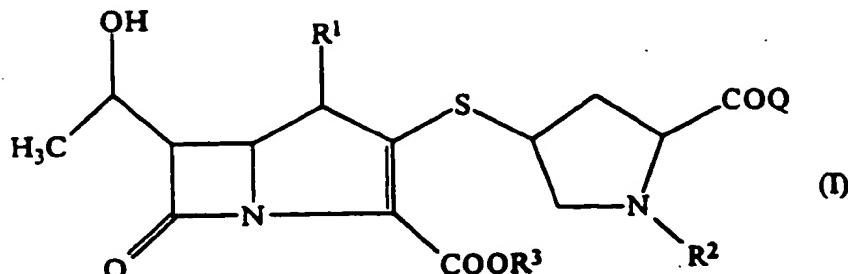
Those carbapenem antibiotics having no substituent at the 1-position are potentially a very useful series of compounds which have extraordinarily potent antibacterial activity. Unfortunately, however, they are chemically unstable and, moreover, are sensitive to dehydropeptidase I *in vivo*. Dehydropeptidase I is an enzyme which hydrolyses the beta-lactam ring in carbapenem antibiotics and which exists in mammalian tissue, for example in the renal cortex. It is responsible for the extensive metabolism of many otherwise valuable beta-lactam antibiotics in animals, including humans, thus greatly reducing their value. Despite these disadvantages, these carbapenem antibiotics are finding increasing use in the treatment of bacterial infections.

Metabolism of the antibiotic *in vivo* may be demonstrated by a low recovery of the compound itself (as opposed to its metabolic products) in the urine, and this has been demonstrated for thienamycin [H. Krupp et al., Antimicrob. Agents. Chemother., 22, 62 (1982); and S. R. Norrby et al., ibid., 23, 300 (1983)].

Although it has been found that carbapenem compounds having a substituent at the 1-position (commonly a 1-methyl group) do not have this susceptibility to dehydropeptidase I *in vivo*, many of the compounds of this type discovered to date lack sufficient activity. It is, therefore, considered highly desirable to find a carbapenem antibiotic which combines the good activity of thienamycin with a resistance to dehydropeptidase I *in vivo*.

Many carbapenem compounds are now known. Some are described, for example, in European Patent Publications No. 126 587, 333 175, 442 497, 443 883, 508 682 and 518 558. European Patent Publication No. 333 175 discloses compounds in which a thio-pyrrolidinyl group and its ring carbon atom substituent are linked by an alkylene group, and thus differ from the compounds of the present invention in that there is no linking carbonyl group. The compounds disclosed in European Patent Publication 126 587, on the other hand, are carboxylic thio-pyrrolidinyl beta-lactam compounds. However, it is thought that the closest prior art to the compounds of the present invention is represented by European Patent Publications No. 508 682 and 518 558, both of which were published after the priority dates hereof. The present compounds have demonstrated significantly better activity than the other prior art compounds.

Thus, the compounds of the present invention are those compounds of formula (I) and pharmaceutically acceptable salts and esters thereof:



in which:

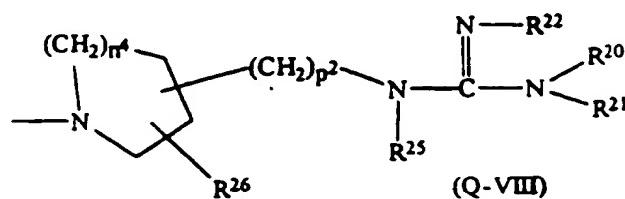
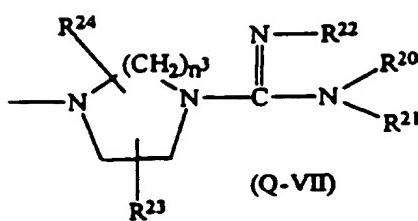
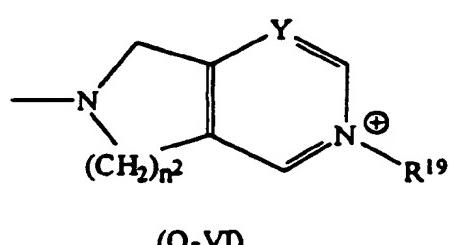
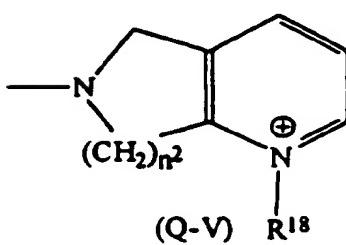
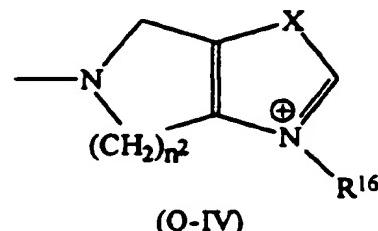
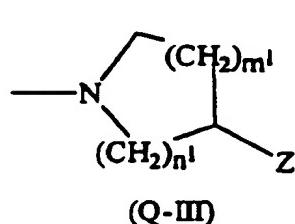
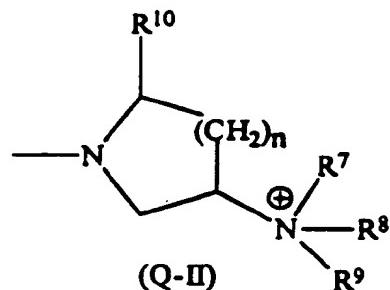
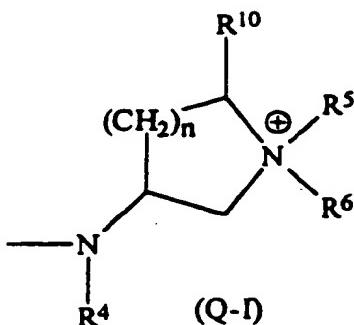
R¹ represents a hydrogen atom or a methyl group;

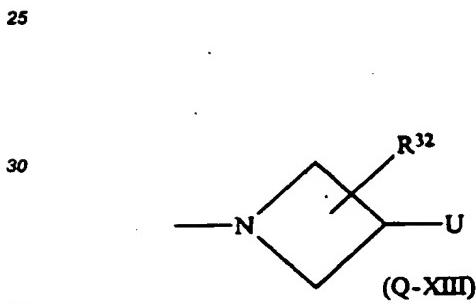
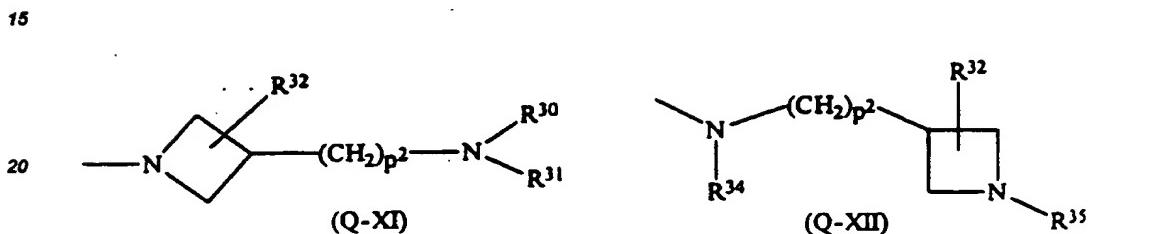
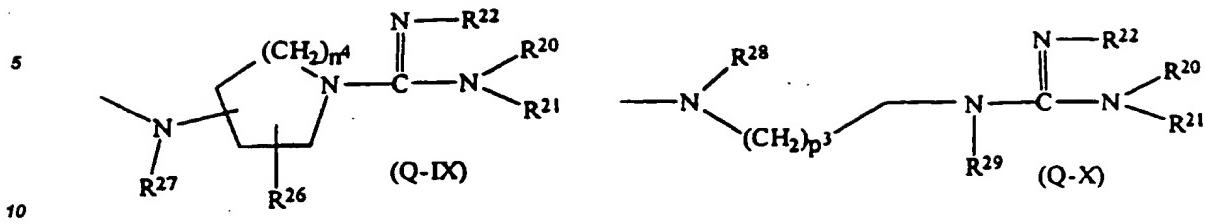
R² represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents A, defined below, an alkenyl group having from 2 to 6 carbon atoms, an alkynyl group having from 2 to 6 carbon atoms, or, provided that Q does not contain a quaternary nitrogen atom, a group of formula -C(=NH)R⁰,

where R⁰ represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

R³ represents a hydrogen atom, a negative ion or a carboxy-protecting group; and

Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-IV), (Q-V), (Q-VI), (Q-VII), (Q-VIII), (Q-IX), (Q-X), (Q-XI), (Q-XII) and (Q-XIII):





wherein:

40 R^4 represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, or a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents B, defined below;

45 R^5 and R^6 are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 6 carbon atoms, and substituted alkyl groups which have from 1 to 6 carbon atoms and which are substituted by at least one of substituents B, defined below;

R^4 and R^6 together represent a group of formula $-(CH_2)_m-$, where m is 2 or 3;

50 R^7 , R^8 and R^9 are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 6 carbon atoms, and substituted alkyl groups which have from 1 to 6 carbon atoms and which are substituted by at least one of substituents B, defined below;

55 R^{10} represents a hydrogen atom, a carbamoyl group, an unsubstituted alkyl group having from 1 to 6 carbon atoms, or a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least n of substituents B, defined below;

or

R^7 and R^8 together represent a group of formula $-(CH_2)_p-(W)_w-(CH_2)_q-$, where p is 0, 1, 2 or 3, q is 0, 1, 2 or 3,

55 W represents an oxygen or sulphur atom and w is 0 or 1, provided that $(p + q + w)$ is an integer from 2 to 6;

or

R^7 and R^{10} together represent a group of formula $-(CH_2)_p-(W)_w-(CH_2)_q-$, where p' is 0, 1, 2 or 3, q' is 0, 1, 2

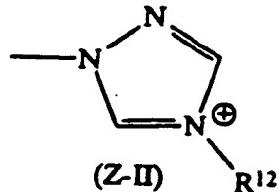
or 3, W represents an oxygen or sulphur atom and w' is 0 or 1 provided that (p' + q' + w') is at least one;
n is 0 or 1;
Z represents a group of formula (Z-I), (Z-II), (Z-III), (Z-IV), (Z-V), (Z-VI), (Z-VII) or (Z-VIII);

5

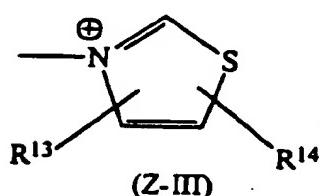


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(Z-I)

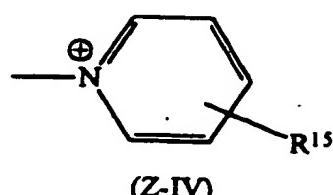


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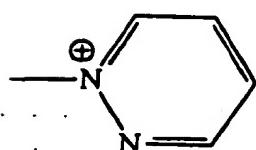
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(Z-III)



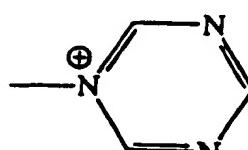
(Z-IV)

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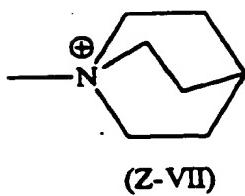
(Z-V)



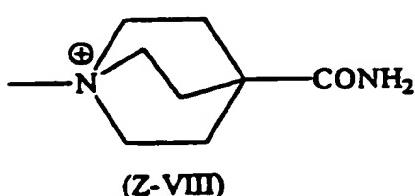
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(Z-VI)

40



(Z-VII)



(Z-VIII)

45

whereto:

R¹¹ and R¹² are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 6 carbon atoms, and substituted alkyl groups which have from 1 to 6 carbon atoms and which are substituted by at least one of substituents B, defined below; and

50

R¹³, R¹⁴ and R¹⁵ are independently selected from the group consisting of carbamoyl groups, unsubstituted alkyl groups having from 1 to 6 carbon atoms, and substituted alkyl groups which have from 1 to 6 carbon atoms and which are substituted by at least one of substituents B, defined below;

m' is 0 or 1 and n' is 0, 1 or 2, provided that (m' + n') is greater than 0;

55

R¹⁶ represents an unsubstituted alkyl group having from 1 to 6 carbon atoms, or a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents B, defined below;

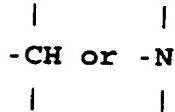
R¹⁷ represents an unsubstituted alkyl group having from 1 to 6 carbon atoms, or a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents B, defined below;

X represents a sulphur atom or a group of formula >NR¹⁷, where R¹⁷ represents an unsubstituted alkyl group

having from 1 to 6 carbon atoms or a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by a single substituent selected from halogen atoms, carbamoyl groups and hydroxy groups; n^2 is 1 or 2;

R^{19} represents an unsubstituted alkyl group having from 1 to 6 carbon atoms, or a substituted alkyl group which

5 has from 1 to 6 carbon atoms and which is substituted by at least one of substituents B, defined below; Y represents a group of formula



R^{20} , R^{21} and R^{22} are independently selected from hydrogen atoms and unsubstituted alkyl groups having from 15 1 to 6 carbon atoms;

or

R^{20} and R^{21} or R^{20} and R^{22} together represent a group of formula $-(CH_2)_s-(W)_{w'}-(CH_2)_t$, where s is 0, 1, 2 or 3, t is 0, 1, 2 or 3, W represents an oxygen or sulphur atom and w' is 0 or 1;

20 R^{23} and R^{24} are independently selected from hydrogen atoms, halogen atoms, unsubstituted alkyl groups having from 1 to 6 carbon atoms, substituted alkyl groups which have from 1 to 6 carbon atoms and which are substituted by at least one of substituents C, defined below, hydroxy groups, carboxy groups, carbamoyl groups, amino groups, cyano groups and carbamoyloxy groups; n^3 is 1, 2 or 3;

25 R^{25} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents C, defined below, an alkenyl group having from 2 to 6 carbon atoms, or an alkynyl group having from 2 to 6 carbon atoms;

30 R^{26} represents a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents C, defined below, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group or a carbamoyloxy group;

n^4 is 0, 1 or 2;

p^2 is 0 or 1;

35 R^{27} represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 6 carbon atoms;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen atoms, unsubstituted alkyl groups having from 1 to 6 carbon atoms, and substituted alkyl groups which have from 1 to 6 carbon atoms and which are substituted by at least one of substituents C, defined below;

p^3 is 1 or 2;

40 R^{30} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents D, defined below, an alkenyl group having from 2 to 6 carbon atoms, an alkynyl group having from 2 to 6 carbon atoms, or a group of formula $-C(=NH)R^{33}$,

45 where R^{33} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents E, defined below, a cycloalkyl group having from 3 to 6 ring carbon atoms or a cycloalkylalkyl group in which the cycloalkyl part has from 3 to 6 ring carbon atoms and the alkyl part has from 1 to 6 carbon atoms;

50 R^{31} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents F, defined below, an alkenyl group having from 2 to 6 carbon atoms, or an alkynyl group having from 2 to 6 carbon atoms;

55 R^{32} represents a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents F, defined below, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group or a carbamoyloxy group;

R^{34} represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 6 carbon atoms;

60 R^{35} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 6 carbon atoms, a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by at least one of substituents G, defined below, an alkenyl group having from 2 to 6 carbon atoms, an alkynyl group having from 2 to 6 carbon atoms, or a group of formula $-C(=NH)R^{33}$, where R^{33} is as defined above; and

U represents an imidazolyl group, a triazolyl group or a tetrazolyl group; substituents A are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyan groups, halogen atoms, oxygen atoms (to form an oxo group), alkoxy groups having from 1 to 6 carbon atoms, amino groups, alkylamino groups having from 1 to 6 carbon atoms and dialkylamino groups in which each alkyl part has from 1 to 6 carbon atoms;

5 substituents B are selected from: cyano groups, hydroxy groups, carboxy groups, sulpho groups, halogen atoms, alkoxy groups having from 1 to 6 carbon atoms, alkylthio groups having from 1 to 6 carbon atoms, alkylsulphinyl groups having from 1 to 6 carbon atoms, alkylsulphonyl groups having from 1 to 6 carbon atoms, alkanoylamino groups having from 1 to 6 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms,

10 alkanoyl groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, ureido groups, carbamoyl groups, alkylcarbamoyl groups having from 2 to 7 carbon atoms, carbamoyloxy groups, alkylcarbamoyloxy groups having from 2 to 7 carbon atoms, dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 6 carbon atoms, amino groups, alkylamino groups having from 1 to 6 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 6 carbon atoms,

15 sulphamoyl groups, oxygen atoms (to form an oxo group) and cycloalkyl groups having from 3 to 6 ring carbon atoms;

substituents C are selected from: hydroxy groups, carboxy groups, carbamoyl groups, cyano groups, halogen atoms, alkoxy groups having from 1 to 6 carbon atoms and amino groups;

20 substituents D are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups, sulphamoyl groups, ureido groups, sulpho groups, alkoxy groups having from 1 to 6 carbon atoms, alkoxycarbonyl groups having from 2 to 7 carbon atoms, alkanoyl groups having from 1 to 6 carbon atoms, alkanoylamino groups having from 1 to 6 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms, halogen atoms, amino groups, alkylamino groups having from 1 to 6 carbon atoms, alkylthio groups having from 1 to 6 carbon atoms, alkylsulphinyl groups having from 1 to 6 carbon atoms, alkylsulphonyl groups

25 having from 1 to 6 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 6 carbon atoms; alkylcarbamoyl groups having from 2 to 7 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 6 carbon atoms, alkylcarbamoyloxy groups having from 2 to 7 carbon atoms and dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 6 carbon atoms;

substituents E are selected from: halogen atoms and alkoxy groups having from 1 to 6 carbon atoms;

30 substituents F are selected from: hydroxy groups, carboxy groups, carbamoyl groups, halogen atoms, alkoxy groups having from 1 to 6 carbon atoms and amino groups; and substituents G are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups, halogen atoms, alkoxy groups having from 1 to 6 carbon atoms and amino groups.

The present invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier, diluent or adjuvant in admixture with an effective amount of an antibiotic, wherein the antibiotic is selected from compounds of formula (I) and pharmaceutically acceptable salts and esters thereof.

The present invention further provides the use of an antibiotic, wherein the antibiotic is selected from compounds of formula (I) and pharmaceutically acceptable salts and esters thereof, as a pharmaceutical.

The present invention also provides processes for preparing these compounds, which are described in greater detail hereafter.

The compounds of the present invention may contain an onium ion (i.e. the nitrogen atom of a quaternary ammonium group) in the groups of formula (Q-I), (Q-II), (Q-IV), (Q-V) and (Q-VI). In this case, it is preferred that R³ should represent a negative ion (i.e. there should be a group of formula -COO⁻ at the carbapenem 3-position), to balance the positively charged onium ion. However, if R³ represents, for example, an ester group, then it is necessary that the compound should contain a negative ion to balance the positive onium ion. Such a negative ion may be provided by the anionic part of any of the acids referred to hereafter.

In the compounds of the present invention, where R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴ or R³⁵ represents an alkyl group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl and isohexyl groups. Of these, we prefer those alkyl groups having from 1 to 4 carbon atoms, preferably the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups, and most preferably the methyl and ethyl groups.

Where R⁰ or R² represents an alkyl group having from 1 to 6 carbon atoms, this may be a straight or branched chain group having from 1 to 6, preferably from 1 to 4, carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 2-methylbutyl, 1-ethyl-

propyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, hexyl and is hexyl groups. Of these, we prefer those alkyl groups having from 1 to 3 carbon atoms, preferably the methyl, ethyl and propyl groups, and most preferably the methyl group.

5 Where R², R²⁶, R³⁰, R³¹ or R³⁶ represents an alkenyl group, this may be a straight or branched chain group having from 2 to 6, preferably 3 or 4, carbon atoms, and examples include the vinyl, allyl, 2-methylallyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butanyl, 3-butanyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl and 3-hexenyl groups, of which the vinyl, allyl, 2-methylallyl, 1-propenyl, isopropenyl and butenyl groups are preferred, the allyl and 2-methylallyl groups being most preferred.

10 Where R², R²⁶, R³⁰, R³¹ or R³⁶ represents an alkynyl group, this may be a straight or branched chain group having from 2 to 6, preferably 3 or 4, carbon atoms, and examples include the ethynyl, propargyl (2-propynyl), 1-propynyl, 2-methylpropargyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl and 3-hexynyl groups, of which the propynyl and 2-methylpropargyl groups are preferred.

15 Where R³³ represents a cycloalkyl group, this has from 3 to 6 ring carbon atoms, and may be a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group, of which the cyclopropyl, cyclobutyl and cyclopentyl groups are preferred.

20 Where R³³ represents a cycloalkylalkyl group, the cycloalkyl part has from 3 to 6 ring carbon atoms and the alkyl part has from 1 to 6 ring carbon atoms. Examples of the alkyl part, which may be a straight or branched chain group, are as given above in relation to R⁴ etc., and examples of the cycloalkyl part are as given above in relation to R³³. Specific examples of such cycloalkylalkyl groups include the cyclopropylmethyl, 1- and 2-cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 3-cyclopropylpropyl, 4-cyclopentylbutyl, 5-cyclopropylpentyl, 6-cyclobutylhexyl, 2-cyclopropylpropyl and 2-cyclopropylbutyl groups, of which the cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl and cyclopentylmethyl groups are preferred.

25 Where R² represents a substituted alkyl group, the alkyl part itself may be any of the alkyl groups exemplified above in relation to the unsubstituted alkyl groups, and the substituents are selected from the group consisting of substituents A, for example:

hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups;

halogen atoms, such as the fluorine, chlorine, bromine or iodine atoms, preferably the fluorine, chlorine or bromine atoms;

oxygen atoms (to form an oxo group);

30 alkoxy groups having from 1 to 6 carbon atoms, which may be straight or branched chain alkoxy groups, and examples include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, neopentyloxy, isopentyloxy and hexyloxy groups, of which we prefer those alkoxy groups having from 1 to 3 carbon atoms, more preferably the methoxy, ethoxy or propoxy group;

35 amino groups;

alkylamino groups having from 1 to 6 carbon atoms, in which the alkyl part may be as exemplified above in relation to R² etc., and examples include the methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, t-butylamino, pentylamino, isopentylamino, neopentylamino, and hexylamino groups, of which we prefer the methylamino, ethylamino and propylamino groups; and

40 dialkylamino groups in which each alkyl part has from 1 to 6 carbon atoms and may be as exemplified above in relation to R² etc.; examples include the dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, dipentylamino, dihexylamino, methylethylamino and methylpropylamino, of which we prefer the dimethylamino, diethylamino and dipropylamino groups.

45 Where R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ or R¹⁸ represents a substituted alkyl group, this has from 1 to 6 carbon atoms and may be any of the alkyl groups exemplified above in relation to the unsubstituted groups represented by these symbols. The substituents may be selected from the group consisting of substituents B, for example:

50 cyano groups, hydroxy groups, carboxy groups, sulpho groups, ureido groups, carbamoyl groups, carbamoyloxy groups, amino groups, sulphamoyl groups and oxygen atoms (to form an oxo group);

halogen atoms, alkoxy groups, alkylamino groups and dialkylamino groups, all as exemplified above in relation to substituents A;

alkylthio groups having from 1 to 6 carbon atoms, in which the alkyl part may be as exemplified above in relation to R² etc., preferably the methylthio, ethylthio or propylthio groups;

55 above in relation to R² etc., preferably the methylsulphinyl, ethylsulphinyl or propylsulphinyl groups;

alkylsulphonyl groups having from 1 to 6 carbon atoms, in which the alkyl part may be as exemplified above in relation to R² etc., preferably the methylsulphonyl, ethylsulphonyl or propylsulphonyl groups;

alkanoylamino groups having from 1 to 6 carbon atoms, which may be a straight or branched chain group;

examples of such groups include the formamido, acetamido, propionamido, butyramido, isobutyramido, valerylamino, isovalerylamino, pivaloylamino and hexanylamino groups, of which the acetamido and propionamido groups are preferred;

5 alkanoyloxy groups having from 1 to 6 carbon atoms, which may be a straight or branched chain group; examples of such groups include the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy and hexanoyloxy groups, of which the acetoxy and propionyloxy groups are preferred;

10 alkanoyl groups having from 1 to 6 carbon atoms, which may be a straight or branched chain group; examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl groups, of which the acetyl and propionyl groups are preferred;

15 alkoxy carbonyl groups having from 2 to 7 carbon atoms, that is the alkoxy part has from 1 to 6 carbon atoms, and examples include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl groups; of these, we prefer those alkoxy carbonyl groups having from 1 to 3 carbon atoms, more preferably the methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl groups;

20 alkylcarbamoyl groups having from 2 to 7 carbon atoms, that is the alkyl part has from 1 to 6 carbon atoms, and examples include the methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, sec-butylcarbamoyl, t-butylcarbamoyl, pentylcarbamoyl, isopentylcarbamoyl, neopentylcarbamoyl, and hexylcarbamoyl groups, of which we prefer the methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl groups;

25 dialkylcarbamoyl groups in which each alkyl part has from 1 to 6 carbon atoms; examples include the dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, dipentylcarbamoyl, dihexylcarbamoyl, methylethylcarbamoyl and methylpropylcarbamoyl groups, of which we prefer the dimethylcarbamoyl, diethylcarbamoyl and dipropylcarbamoyl groups;

30 alkylcarbamoyloxy groups having from 2 to 7 carbon atoms, that is the alkyl part has from 1 to 6 carbon atoms, and examples include the methylcarbamoyloxy, ethylcarbamoyloxy, propylcarbamoyloxy, isopropylcarbamoyloxy, butylcarbamoyloxy, isobutylcarbamoyloxy, sec-butylcarbamoyloxy, t-butylcarbamoyloxy, pentylcarbamoyloxy, isopentylcarbamoyloxy, neopentylcarbamoyloxy, and hexylcarbamoyloxy groups, of which we prefer the methylcarbamoyloxy, ethylcarbamoyloxy and propylcarbamoyloxy groups; and

35 dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 6 carbon atoms; examples include the dimethylcarbamoyloxy, diethylcarbamoyloxy, dipropylcarbamoyloxy, diisopropylcarbamoyloxy, dibutylcarbamoyloxy, dipentylcarbamoyloxy, dihexylcarbamoyloxy, methylethylcarbamoyloxy and methylpropylcarbamoyloxy groups, of which we prefer the dimethylcarbamoyloxy, diethylcarbamoyloxy and dipropylcarbamoyloxy groups.

40 In the case of substituents C, D, E, F and G, examples of the groups and atoms which may be included in these are as given in relation to the equivalent groups and atoms of substituents B.

Where R³ represents a carboxy-protecting group, this is preferably a group capable of forming an ester with a carboxylic acid. Examples of ester groups include:

45 alkyl groups having from 1 to 20 carbon atoms, more preferably from 1 to 6 carbon atoms, such as those exemplified in relation to substituents R⁴ and higher alkyl groups as are well known in the art, such as the heptyl, octyl, nonyl, decyl, dodecyl, tridecyl, pentadecyl, octadecyl, nonadecyl andicosyl groups, but preferably groups having from 1 to 4 carbon atoms and most preferably the methyl, ethyl and t-butyl groups;

50 cycloalkyl groups having from 3 to 7 carbon atoms, for example the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups;

55 aralkyl groups, in which the alkyl part has from 1 to 3 carbon atoms and the aryl part is a carbocyclic aromatic group having from 6 to 14 carbon atoms, which may be substituted or unsubstituted and, if substituted, has at least one of substituents H defined and exemplified below, although the unsubstituted groups are preferred; examples of such aralkyl groups include the benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, benzhydryl (i.e. diphenylmethyl), triphenylmethyl, bis(o-nitrophenyl)methyl, 9-anthrylmethyl, 2,4,6-trimethylbenzyl, 4-bromobenzyl, 2-nitrobenzyl, 4-nitrobenzyl, 3-nitrobenzyl, 4-methoxybenzyl and piperonyl groups, of which the benzyl, benzhydryl, 4-nitrobenzyl and 2-nitrobenzyl groups are preferred;

60 alkenyl groups having from 2 to 6 carbon atoms, and halogenated alkenyl groups having from 2 to 6 carbon atoms, such as the vinyl, allyl, 2-methylallyl, 2-chloroallyl, 1-propenyl, isopropenyl, 1-but enyl, 2-but enyl, 3-but enyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl groups, of which the vinyl, allyl, 2-methylallyl, 1-propenyl, isopropenyl and butenyl groups are preferred, the allyl, 2-chloroallyl and 2-methylallyl groups being most preferred.

halogenated alkyl groups having from 1 to 6, preferably from 1 to 4, carbon atoms, in which the alkyl

part is as defined and exemplified in relation to the alkyl groups above, and the halogen atom is chlorine, fluorine, bromine or iodine (preferably chlorine or bromine), such as the 2,2,2-trichloroethyl, 2-haloethyl (e.g. 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl or 2-iodoethyl), 2,2-dibromoethyl and 2,2,2-tribromoethyl groups, preferably the 2,2,2-trichloroethyl, 2,2-dibromoethyl and 2,2,2-tribromoethyl groups;

5 substituted silylalkyl groups, in which the alkyl part is as defined and exemplified above, and the silyl group has up to 3 substituents selected from alkyl groups having from 1 to 6 carbon atoms and phenyl groups which are unsubstituted or have at least one substituent selected from substituents H defined and exemplified below, for example a 2-trimethylsilylethyl group;

10 phenyl groups, in which the phenyl group is unsubstituted or substituted, preferably with at least one alkyl group having from 1 to 4 carbon atoms or acylamino group, for example the phenyl, tolyl and benzamidophenyl groups;

phenacyl groups, which may be unsubstituted or have at least one of substituents H defined and exemplified below, for example the phenacyl group itself or the ρ -bromophenacyl group;

15 cyclic and acyclic terpenyl groups, for example the geranyl, neryl, linalyl, phytyl, menthyl (especially m - and ρ -menthyl), thujyl, caryl, pinanyl, bornyl, notcaryl, norpinanyl, norbornyl, menthenyl, camphenyl and norbornenyl groups;

20 alkoxymethyl groups, in which the alkoxy part has from 1 to 6, preferably from 1 to 4, carbon atoms and may itself be substituted by a single unsubstituted alkoxy group, such as the methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl and methoxyethoxymethyl groups;

25 aliphatic acyloxyalkyl groups, in which the acyl group is preferably an alkanoyl group and is more preferably an alkanoyl group having from 2 to 6 carbon atoms, and the alkyl part has from 1 to 6, and preferably from 1 to 4, carbon atoms such as the acetoxyethyl, propionyloxymethyl, butyryloxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, 1-pivaloyloxyethyl, 1-acetoxyethyl, 1-isobutyryloxyethyl, 1-pivaloyloxypropyl, 2-methyl-1-pivaloyloxypropyl, 2-pivaloyloxypropyl, 1-isobutyryloxyethyl, 1-isobutyryloxypropyl, 1-acetoxypyl, 1-acetoxy-2-methylpropyl, 1-propionyloxethyl, 1-propionyloxypyl, 2-acetoxypyl and 1-butyryloxyethyl groups, preferably a pivaloyloxymethyl, isobutyryloxymethyl, 1-isobutyryloxyethyl, acetoxyethyl or 1-acetoxyethyl group;

30 cycloalkyl-substituted aliphatic acyloxyalkyl groups, in which the acyl group is preferably an alkanoyl group and is more preferably an alkanoyl group having from 2 to 6 carbon atoms, the cycloalkyl substituent has from 3 to 7 carbon atoms, and the alkyl part has from 1 to 6, preferably from 1 to 4, carbon atoms, such as the (cyclohexylacetoxyl)methyl, 1-(cyclohexylacetoxyl)ethyl, 1-(cyclohexylacetoxyl)propyl, 2-methyl-1-(cyclohexylacetoxyl)propyl, (cyclopentylacetoxyl)methyl, 1-(cyclopentylacetoxyl)ethyl, 1-(cyclopentylacetoxyl)propyl and 2-methyl-1-(cyclopentylacetoxyl)propyl, groups;

35 alkoxy carbonyloxyalkyl groups, especially 1-(alkoxy carbonyloxy)ethyl groups, in which the alkoxy part has from 1 to 10, preferably from 1 to 6, and more preferably from 1 to 4, carbon atoms, and the alkyl part has from 1 to 8, preferably from 1 to 4, carbon atoms, such as the t-butoxycarbonyloxyethyl, 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-propoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl, 1-butoxycarbonyloxyethyl, 1-isobutoxycarbonyloxyethyl, 1-sec-butoxycarbonyloxyethyl, 1-t-butoxycarbonyloxyethyl, 1-(1-ethylpropoxycarbonyloxy)ethyl and 1-(1,1-dipropylbutoxycarbonyloxy)ethyl groups, and other alkoxy carbonylalkyl groups, in which both the alkoxy and alkyl groups have from 1 to 6, preferably from 1 to 4, carbon atoms, such as the 2-methyl-1-(isopropoxycarbonyloxy)propyl, 2-(isopropoxycarbonyloxy)propyl, isopropoxycarbonyloxyethyl, t-butoxycarbonyloxyethyl, methoxycarbonyloxyethyl and ethoxycarbonyloxyethyl groups; of these, the t-butoxycarbonyloxyethyl, 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl, 1-isopropoxycarbonyloxyethyl and 1-t-butoxycarbonyloxyethyl groups are preferred;

45 cycloalkylcarbonyloxyalkyl and cycloalkyloxycarbonyloxyalkyl groups, in which the cycloalkyl group has from 3 to 10, preferably from 3 to 7, carbon atoms, is mono- or poly-cyclic and is optionally substituted by at least one (and preferably only one) alkyl group having from 1 to 4 carbon atoms (e.g. selected from those alkyl groups exemplified above) and the alkyl part has from 1 to 6, more preferably from 1 to 4, carbon atoms (e.g. selected from those alkyl groups exemplified above) and is most preferably methyl, ethyl or propyl, for example

50 the 1-methylcyclohexylcarbonyloxyethyl, 1-methylcyclohexyloxycarbonyloxyethyl, cyclopentyloxycarbonyloxyethyl, cyclopentylcarbonyloxyethyl, 1-cyclohexyloxycarbonyloxyethyl, 1-cyclohexylcarbonyloxyethyl, 1-cyclopentyloxycarbonyloxyethyl, 1-cyclopentylcarbonyloxyethyl, 1-cycloheptyloxycarbonyloxyethyl, 1-methylcyclopentyloxycarbonyloxyethyl, 1-methylcyclopentylcarbonyloxyethyl, 1-(1-methylcyclohexylcarbonyloxy)propyl, 2-(1-methylcyclohexylcarbonyloxy)propyl, 1-(cyclohexylcarbonyloxy)propyl, 2-(cyclohexylcarbonyloxy)propyl, 2-

55 methyl-1-(1-methylcyclopentylcarbonyloxy)propyl, 1-(1-methylcyclopentylcarbonyloxy)propyl, 2-(1-methylcyclopentylcarbonyloxy)propyl, 1-(cyclopentylcarbonyloxy)propyl, 2-(cyclopentylcarbonyloxy)propyl, 1-(1-methylcyclopentylcarbonyloxy)ethyl, 1-(1-methylcyclopentylcarbonyloxy)propyl, adamantlyloxycarbonyloxy-

thyl, adamantylcarbonyloxymethyl, 1-adamantyloxycarbonyloxyethyl and 1-adamantylcarbonyloxyethyl groups, preferably the 1-cyclohexylcarbonyloxyethyl or 1-cyclopentylcarbonyloxyethyl group;

5 cycloalkylalkoxycarbonyloxyalkyl groups in which the alkoxy group has a single cycloalkyl substituent, the cycloalkyl substituent having from 3 to 10, preferably from 3 to 7, carbon atoms and mono- or poly- cyclic, for example the cyclopropylmethoxycarbonyloxymethyl, cyclobutylmethoxycarbonyloxymethyl, cyclopentylmethoxycarbonyloxymethyl, cyclohexylmethoxycarbonyloxymethyl, 1-(cyclopropylmethoxycarbonyloxy)ethyl, 1-(cyclobutylmethoxycarbonyloxy)ethyl, 1-(cyclopentylmethoxycarbonyloxy)ethyl and 1-(cyclohexylmethoxycarbonyloxy)ethyl groups;

10 terpenylcarbonyloxyalkyl and terpenyloxycarbonyloxyalkyl groups, in which the terpenyl group is as exemplified above, and is preferably a cyclic terpenyl group, for example the 1-(menthyloxycarbonyloxy)ethyl, 1-(menthylcarbonyloxy)ethyl, menthyloxycarbonyloxymethyl, menthylcarbonyloxymethyl, 1-(3-pinanyloxy-carbonyloxy)ethyl, 1-(3-pinanylcarbonyloxy)ethyl, 3-pinanyloxycarbonyloxymethyl and 3-pinanylcarbonyloxy-methyl groups;

15 5-alkyl or 5-phenyl [which may be substituted by at least one of substituents C, defined and exemplified above] (2-oxo-1,3-dioxolen-4-yl)alkyl groups in which each alkyl group (which may be the same or different) has from 1 to 6, preferably from 1 to 4, carbon atoms, for example the (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and 1-(5-methyl-2-oxo-1,3-dioxolen-4-yl)ethyl groups; and

20 other groups, especially groups which are easily removed in vivo such as the phthalidyl, indanyl and 2-oxo-4,5,6,7-tetrahydro-1,3-benzodioxolen-4-yl groups.

Substituents H are selected from hydroxy groups, carboxy groups, carbamoyl groups, cyano groups, halogen atoms, nitro groups, amino groups, alkyl groups having from 1 to 6 carbon atoms and alkoxy groups having from 1 to 6 carbon atoms.

When substituent H represents an alkyl group having from 1 to 6 carbon atoms, this may be as exemplified above in relation to the unsubstituted alkyl groups.

When substituent H represents an alkoxy group having from 1 to 6 carbon atoms, this may be any such group as exemplified in relation to substituents A, hereinabove.

Of the above groups, we especially prefer those groups which can be removed easily in vivo, and most preferably the aliphatic acyloxyalkyl groups (especially the pivaloyloxymethyl group), alkoxy carbonyloxyalkyl groups (especially the 1-isopropoxycarbonyloxyethyl group), cycloalkylcarbonyloxyalkyl groups (especially the 1-methylcyclohexylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl groups), phthalidyl groups and (5-substituted 2-oxo-1,3-dioxolen-4-yl)methyl groups [especially the (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group].

In general, in the compounds of the present invention, R¹ may represent a hydrogen atom or a methyl group, preferably a methyl group.

The compounds of the present invention can form salts. Examples of such salts include: salts with an alkali metal, such as sodium, potassium or lithium; salts with an alkaline earth metal, such as barium or calcium; salts with another metal, such as magnesium or aluminium; ammonium salts; organic base salts, such as a salt with triethylamine, diisopropylamine, cyclohexylamine or dicyclohexylamine; and salts with a basic amino acid, such as lysine or arginine. Also, where the compound of the present invention contains a basic group in its molecule, it can form acid addition salts. Examples of such acid addition salts include: salts with mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulphuric acid or phosphoric acid; salts with lower alkylsulphonic acids, such as methanesulphonic acid, trifluoromethane-sulphonic acid or ethanesulphonic acid; salts with arylsulphonic acids, such as benzenesulphonic acid or p-toluenesulphonic acid; salts with organic carboxylic acids, such as acetic acid, fumaric acid, tartaric acid, oxalic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid or citric acid; and salts with amino acids, such as glutamic acid or aspartic acid.

The compounds of the present invention necessarily contain at least one and possibly several asymmetric carbon atoms in their molecules, and can thus form optical isomers. Although these are all represented herein by a single molecular formula, the present invention includes both the individual, isolated isomers and mixtures, including racemates thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques.

55 The isomers preferably include compounds wherein R¹ represents a methyl group and the 1-position is of the R-configuration; compounds in which the 5- and 6-positions are of the (5S,6S) configuration, which is the same configuration as that of thienamycin; and the α-position having the hydroxy group of the 6-position substituent is of the R-configuration.

Of the compounds of the present invention, a preferred class of compounds are those compound of formula (I) and pharmaceutically acceptable salts and esters thereof, in which:

R¹ represents a hydrogen atom or a methyl group;

5 R² represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents A¹, defined below, an alkenyl group having 3 or 4 carbon atoms, an alkynyl group having 3 or 4 carbon atoms, or, provided that Q does not contain a quaternary nitrogen atom, a group of formula -C(=NH)R⁰,

where R⁰ represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms;

10 R³ represents a hydrogen atom or a negative ion; and

Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-IV), (Q-V), (Q-VI), (Q-VII), (Q-VIII), (Q-IX), (Q-X), (Q-XI), (Q-XII) and (Q-XIII), defined above, wherein:

15 R⁴ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

R⁵ and R⁶ are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B¹, defined below;

or

20 R⁴ and R⁵ together represent a group of formula -(CH₂)_m- where m is 2 or 3;

R⁷, R⁸ and R⁹ are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B¹, defined below;

25 R¹⁰ represents a hydrogen atom, a carbamoyl group, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

or

30 R⁷ and R⁸ together represent a group of formula -(CH₂)_p-(W)_w-(CH₂)_q-, where p is 0, 1, 2 or 3, q is 0, 1, 2 or 3, W represents an oxygen or sulphur atom and w is 0 or 1, provided that (p + q + w) is an integer from 2 to 6;

or

35 R⁷ and R¹⁰ together represent a group of formula -(CH₂)_p-(W)_w-(CH₂)_q-, where p' is 0, 1, 2 or 3, q' is 0, 1, 2 or 3, W represents an oxygen or sulphur atom and w' is 0 or 1;

n is 0 or 1;

Z represents a group of formula (Z-I), (Z-II), (Z-III), (Z-IV), (Z-V), (Z-VI), (Z-VII) or (Z-VIII), defined above, wherein:

40 R¹¹ and R¹² are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B¹, defined below; and

R¹³, R¹⁴ and R¹⁵ are independently selected from the group consisting of carbamoyl groups, unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B¹, defined below;

45 m¹ is 0 or 1 and n¹ is 0, 1 or 2, provided that (m¹ + n¹) is greater than 0;

R¹⁶ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

50 R¹⁸ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

X represents a sulphur atom or a group of formula >NR¹⁷, where R¹⁷ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of carbamoyl groups and hydroxy groups;

n² is 1 or 2;

Y represents a group of formula

R^{20} , R^{21} and R^{22} are independently selected from the group consisting of hydrogen atoms and unsubstituted alkyl groups having from 1 to 3 carbon atoms;

or

R^{20} and R^{21} or R^{20} and R^{22} together represent a group of formula $-(CH_2)_s-(W)_w-(CH_2)_t$, where s is 1 or 2, t is 1 or 2, W represents an oxygen or sulphur atom and w is 0 or 1, provided that $(s + w + t)$ is 2, 3 or 4;

R^{23} and R^{24} are independently selected from the group consisting of hydrogen atoms, halogen atoms, unsubstituted alkyl groups having from 1 to 3 carbon atoms, substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents C^1 defined below, hydroxy groups, carboxy groups, carbamoyl groups, amino groups, cyano groups and carbamoyloxy groups;

10 n^3 is 1, 2 or 3;

R^{25} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents C^1 , defined below, an alkenyl group having 3 or 4 carbon atoms, or an alkynyl group having 3 or 4 carbon atoms;

15 R^{26} represents a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents C^1 , defined below, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group or a carbamoyloxy group;

n^4 is 0, 1 or 2;

p^2 is 0 or 1;

20 R^{27} represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen atoms, unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents C^1 , defined below;

p^3 is 1 or 2;

25 R^{30} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents D^1 , defined below, an alkenyl group having 3 or 4 carbon atoms, an alkynyl group having 3 or 4 carbon atoms, or a group of formula $-C(=NH)R^{33}$,

where R^{33} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms,

30 a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of halogen atoms and alkoxy groups having from 1 to 3 carbon atoms, a cycloalkyl group having from 3 to 6 ring carbon atoms or a cycloalkylalkyl group in which the cycloalkyl part has from 3 to 6 ring carbon atoms and the alkyl part has 1 or 2 carbon atoms;

R^{31} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents F^1 , defined below, an alkenyl group having 3 or 4 carbon atoms, or an alkynyl group having 3 or 4 carbon atoms;

R^{32} represents a hydrogen atom, a halogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

R^{34} represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

40 R^{35} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents G^1 , defined below, an alkenyl group having 3 or 4 carbon atoms, an alkynyl group having 3 or 4 carbon atoms, or a group of formula $-C(=NH)R^{33}$, where R^{33} is as defined above; and

U represents an imidazolyl group, a triazolyl group or a tetrazolyl group;

45 substituents A^1 are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups, halogen atoms and amino groups;

substituents B^1 are selected from: cyano groups, hydroxy groups, carboxy groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms, alkylthio groups having from 1 to 3 carbon atoms, alkylsulphinyl groups having from 1 to 3 carbon atoms, alkylsulphonyl groups having from 1 to 3 carbon atoms, alkanoylamino groups having from 1 to 5 carbon atoms, alkanoyloxy groups having from 1 to 5 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, alkoxycarbonyl groups having from 2 to 5 carbon atoms, ureido groups, carbamoyl groups, alkylcarbamoyl groups having from 2 to 5 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 3 carbon atoms, carbamoyloxy groups, alkylcarbamoyloxy groups having from 2 to 5 carbon atoms, dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 4 carbon atoms, amino groups, alkylamino groups having from 1 to 4 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 4 carbon atoms, oxygen atoms (to form an oxo group) and cycloalkyl groups having from 3 to 6 ring carbon atoms;

55 substituents C^1 are selected from: hydroxy groups, carboxy groups, carbamoyl groups, halogen atoms and ami-

n groups;

substituents D¹ are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups, ureido groups, alkoxy groups having from 1 to 3 carbon atoms, alkoxy carbonyl groups having from 2 to 5 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, alkanoylamino groups having from

5 1 to 5 carbon atoms, alkanoyloxy groups having from 1 to 5 carbon atoms, halogen atoms, amino groups, alkylamino groups having from 1 to 3 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 3 carbon atoms, alkylcarbamoyl groups having from 2 to 5 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 3 carbon atoms, alkylcarbamoyloxy groups having from 2 to 5 carbon atoms and dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 3 carbon atoms;

10 substituents F¹ are selected from: hydroxy groups, carboxy groups, carbamoyl groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms and amino groups; and

substituents G¹ are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms and amino groups.

A more preferred class of compounds are those compounds of formula (I) and pharmaceutically acceptable salts and esters thereof, in which:

R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents A², defined below, or, provided that Q does not contain a quaternary nitrogen atom, a group of formula -C(=NH)R⁰,

20 where R⁰ represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms;

R³ represents a hydrogen atom or a negative ion; and

Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-IV), (Q-V), (Q-VI), (Q-VII), (Q-VIII), (Q-IX), (Q-X), (Q-XI), (Q-XII) and (Q-XIII), defined above, wherein:

25 R⁴ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B², defined below;

R⁵ and R⁶ are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B², defined below;

30 R⁴ and R⁵ together represent a group of formula -(CH₂)_m- , where m is 2 or 3;

R⁷, R⁸ and R⁹ are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B², defined below;

35 R¹⁰ represents a hydrogen atom, a carbamoyl group, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of hydroxy groups, amino groups and halogen atoms;

or

40 R⁷ and R⁸ together represent a group of formula -(CH₂)_p-(W)_w(CH₂)_q- , where p is 1 or 2, q is 1, 2 or 3, W represents an oxygen or sulphur atom and w is 0 or 1, provided that (p + q + w) is an integer from 4 to 6;

or

45 R⁷ and R¹⁰ together represent a group of formula -(CH₂)_p- , where p' is 1, 2 or 3;

n is 0 or 1;

Z represents a group of formula (Z-I), (Z-II), (Z-III), (Z-IV), (Z-V), (Z-VI), (Z-VII) or (Z-VIII), defined above, wherein:

50 R¹¹ and R¹² are independently selected from the group consisting of unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B², defined below; and

R¹³, R¹⁴ and R¹⁵ are independently selected from the group consisting of carbamoyl groups, unsubstituted alkyl groups having from 1 to 3 carbon atoms, and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of substituents B², defined below;

55 m¹ is 0 or 1 and n¹ is 0, 1 or 2, provided that (m¹ + n¹) is an integer from 1 to 3;

R¹⁶ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B², defined below;

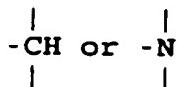
R¹⁸ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B², defined below;

X represents a sulphur atom or a group of formula >NR¹⁷, where R¹⁷ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of carbamoyl groups and hydroxy groups;

n² is 1 or 2;

R¹⁹ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of carbamoyl groups and hydroxy groups; Y represents a group of formula

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R²⁰, R²¹ and R²² are independently selected from the group consisting of hydrogen atoms and unsubstituted alkyl groups having from 1 to 3 carbon atoms;

or

R²⁰ and R²¹ or R²⁰ and R²² together represent a group of formula -(CH₂)_s-(W)_w-(CH₂)_t, where s is 1 or 2, t is 1 or 2, W represents an oxygen or sulphur atom and w' is 0 or 1, provided that (s + w' + t) is 2, 3 or 4;

15

R²³ and R²⁴ are independently selected from the group consisting of hydrogen atoms, halogen atoms, hydroxy groups, carbamoyl groups, carboxy groups, unsubstituted alkyl groups having from 1 to 3 carbon atoms and substituted alkyl groups which have from 1 to 3 carbon atoms and which are substituted by at least one of hydroxy groups, amino groups and carbamoyl groups;

20

n³ is 1, 2 or 3;

R²⁵ represents a hydrogen atom or a methyl group;

R²⁶ represents a hydrogen atom;

n⁴ is 0, 1 or 2;

p² is 0 or 1;

25

R²⁷ represents a hydrogen atom or a methyl group;

R²⁸ and R²⁹ are independently selected from the group consisting of hydrogen atoms and methyl groups;

p³ is 1 or 2;

R³⁰ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents D²,

30

defined below, an alkenyl group having 3 carbon atoms, an alkynyl group having 3 carbon atoms, or a group of formula -C(=NH)R³³,

where R³³ represents a hydrogen atom, a methyl group, a substituted alkyl group which has 1 or 2 carbon atoms and which is substituted by at least one of halogen atoms and methoxy groups, a cyclopropyl group or a cyclopropylmethyl group;

35

R³¹ represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

R³² represents a hydrogen atom;

R³⁴ represents a hydrogen atom or a methyl group;

R³⁵ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents G²,

40

defined below, or a group of formula -C(=NH)R³³, where R³³ is as defined above; and

U represents an imidazolyl group, a triazolyl group or a tetrazolyl group;

substituents A² are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms and amino groups;

substituents B² are selected from: cyano groups, hydroxy groups, carboxy groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms, alkanoylamino groups having from 1 to 5 carbon atoms, alkanoyloxy

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groups having from 1 to 5 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, alkoxy carbonyl groups having from 2 to 5 carbon atoms, ureido groups, carbamoyl groups, alkylcarbamoyl groups having from

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2 to 5 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 3 carbon atoms, carbamoyloxy groups, alkylcarbamoyloxy groups having from 2 to 5 carbon atoms, dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 4 carbon atoms, amino groups, alkylamino groups having from 1 to 4 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 4 carbon atoms and cycloalkyl groups having from 3 to 6 ring carbon atoms;

substituents D² are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyl xy groups, halogen atoms, amino groups, alkylamino groups having from 1 to 3 carbon atoms and dialkylamin groups in

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which each alkyl part has from 1 to 3 carbon atoms;

substituents G² are selected from: hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms, methoxy groups and amino groups.

Of these, we still more prefer those in which Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-VII),

(Q-VIII) and (Q-XI), more especially a group of formula (Q-II), (Q-III), (Q-VII) and (Q-XI).

Of all of these compounds, the most preferred are those in which R¹ represents a methyl group.

Specific examples of the compounds of the present invention are shown in the following formula (I-1) and (I-2). In these formulae, Q is as defined in Tables 1 to 13; Tables 1 to 6 relate to formula (I-1), and Tables 7 to 13 relate to formula (I-2). In each of the examples given in Tables 1 to 6, each of R¹ and R² can be a hydrogen atom or a methyl group, i.e. each of the options shown represents 4 possibilities, that is:

(a) R¹ = hydrogen, R² = hydrogen;

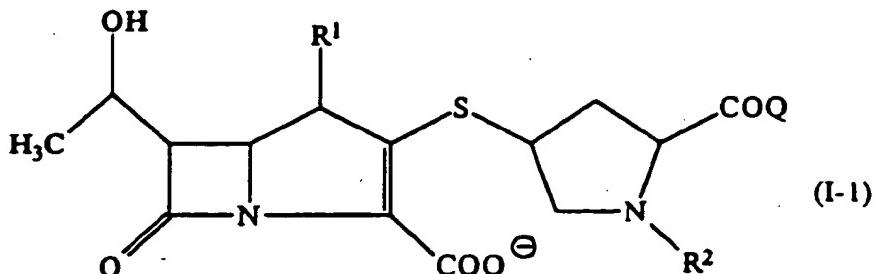
(b) R¹ = methyl, R² = hydrogen;

(c) R¹ = hydrogen, R² = methyl;

(d) R¹ = methyl, R² = methyl.

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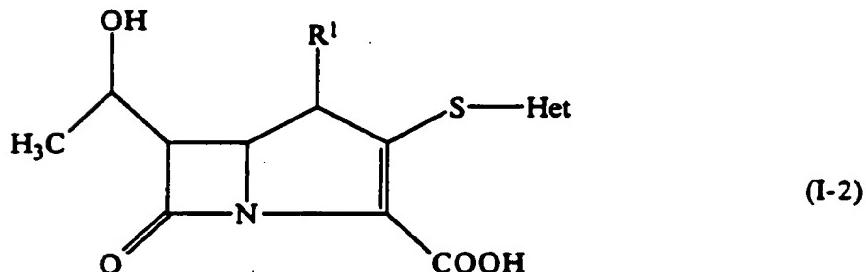


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Table I

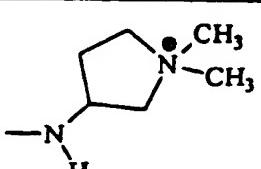
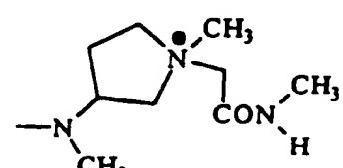
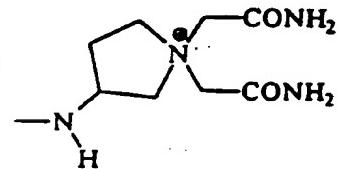
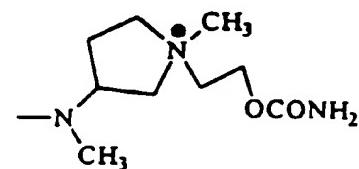
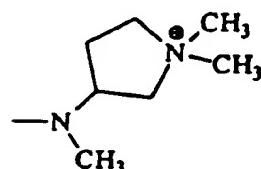
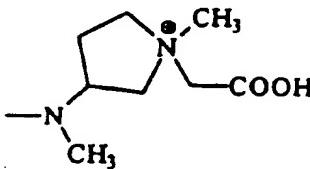
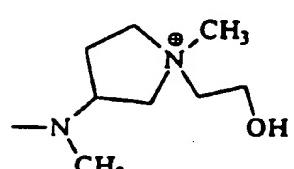
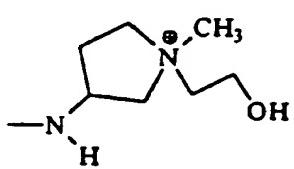
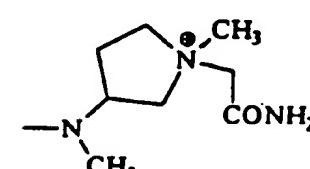
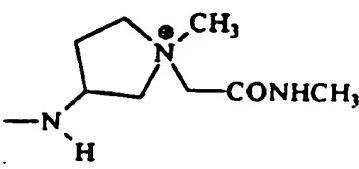
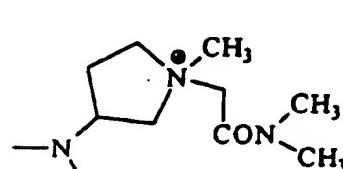
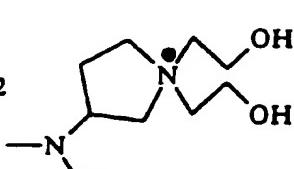
5	Compound No.	Q	Compound No.	Q
10	I-1		I-7	
15	I-2		I-8	
20	I-3		I-9	
25	I-4		I-10	
30	I-5		I-11	
35	I-6		I-12	
40				
45				
50				
55				

Table I (cont.)

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	Compound No.	Q	Compound No.	Q
10	1-13		1-19	
15	1-14		1-20	
20	1-15		1-21	
25	1-16		1-22	
30	1-17		1-23	
35	1-18		1-24	
40				
45				
50				
55				

Table I (cont.)

5 Compound No.	Q	Compound No.	Q
10 1-25		1-31	
15 1-26		1-32	
20 1-27		1-33	
25 1-28		1-34	
30 1-29		1-35	
35 1-30		1-36	
40			
45			
50			
55			

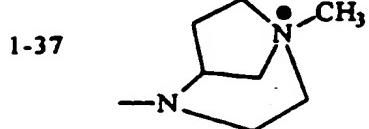
Table 1 (cont.)

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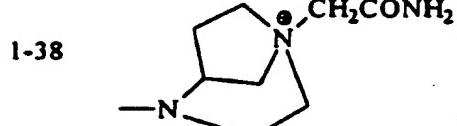
Compound
No.

Q

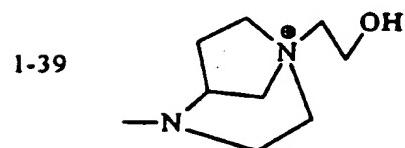
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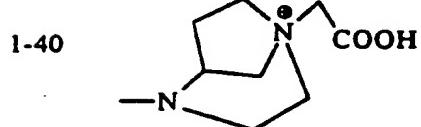
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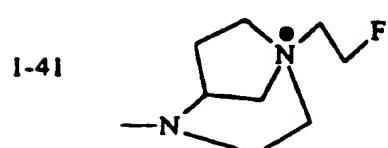
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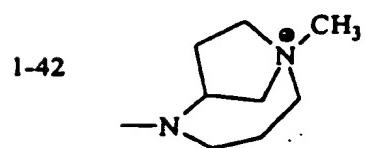
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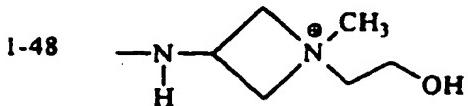
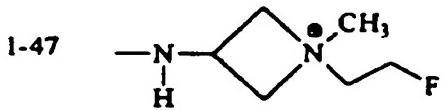
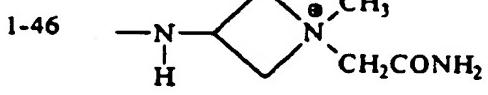
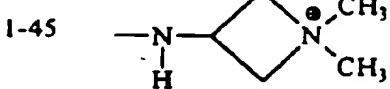
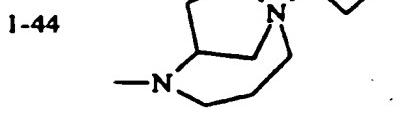
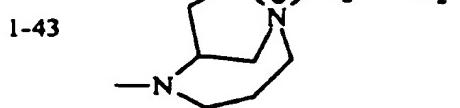
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Compound
No.

Q



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Table I (cont.)

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Compound
No.

Q

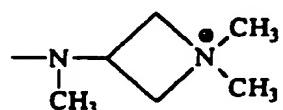
Compound
No.

Q

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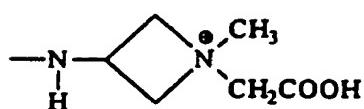
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1-49



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1-50



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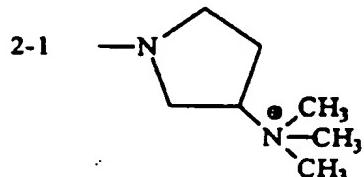
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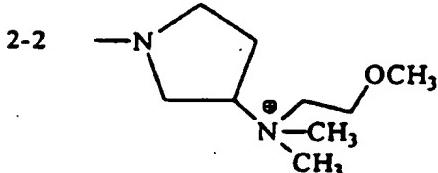
Compound
No.

Q

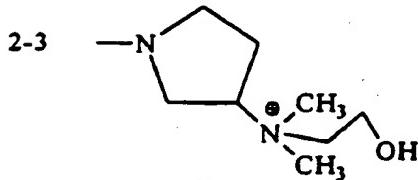
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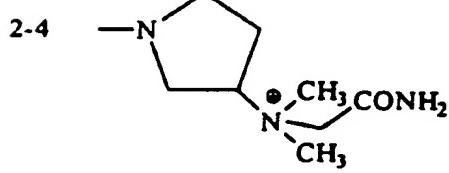
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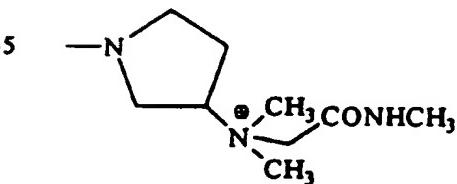
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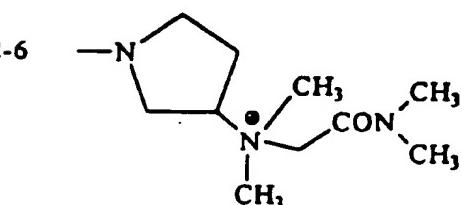
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Compound
No.

Q

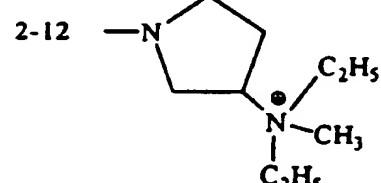
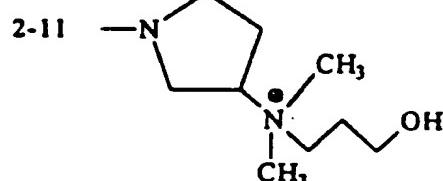
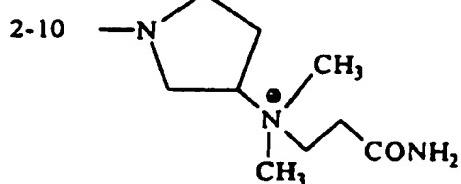
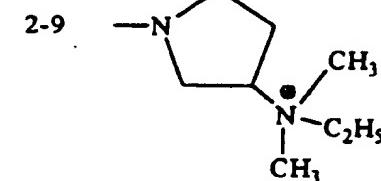
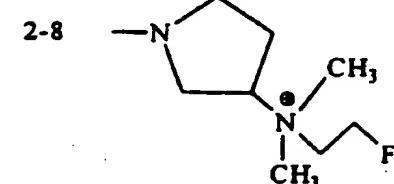
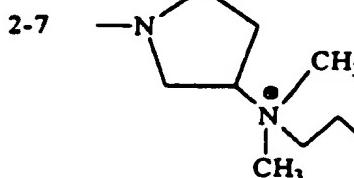


Table 2 (cont.)

5	Compound No.	Q	Compound No.	Q
10	2-13		2-19	
15	2-14		2-20	
20	2-15		2-21	
25	2-16		2-22	
30	2-17		2-23	
35	2-18		2-24	
40				
45				
50				
55				

Table 2 (cont.)

5	Compound No.	Q	Compound No.	Q
10	2-25		2-31	
15	2-26		2-32	
20	2-27		2-33	
25	2-28		2-34	
30	2-29		2-35	
35	2-30		2-36	
40				
45				
50				
55				

Table 2 (cont.)

5	Compound No.	Q	Compound No.	Q
10	2-37		2-42	
15				
20	2-38		2-43	
25	2-39		2-44	
30			2-45	
35	2-40		2-46	
40			2-47	
45	2-41		2-48	
50				
55				

Table 2 (cont.)

5	Compound No.	Q	Compound No.	Q
10	2-49		2-55	
15	2-50		2-56	
20				
25	2-51		2-57	
30	2-52			
35	2-53			
40				
45	2-54			
50				
55				

Table 3

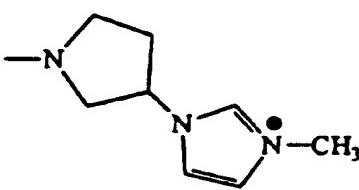
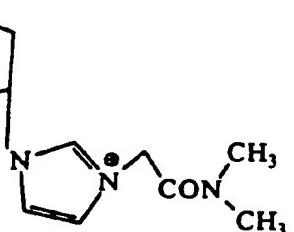
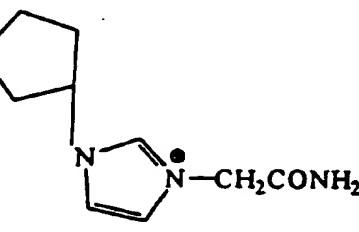
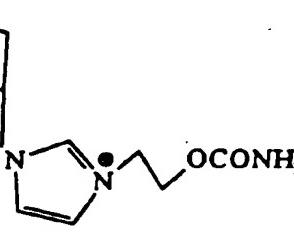
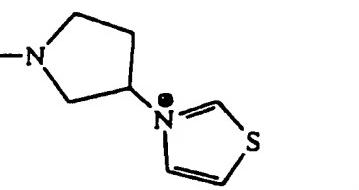
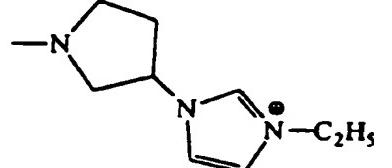
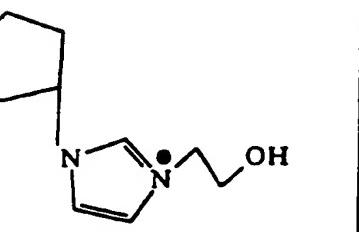
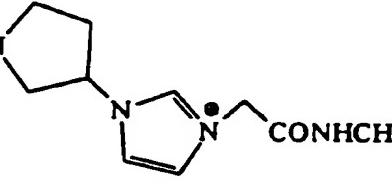
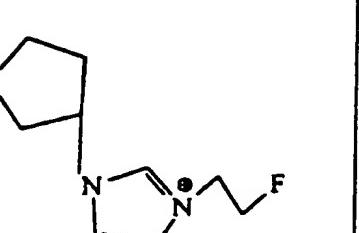
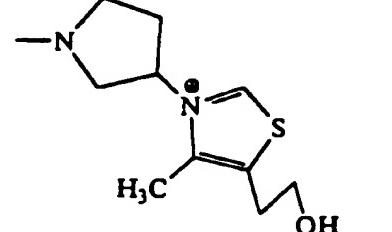
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10 3-1		3-6	
15 3-2		3-7	
20 3-3		3-8	
25 3-4		3-9	
30 3-5		3-10	
35 40 45 50 55			

Table 3 (cont.)

5	Compound No.	Q	Compound No.	Q
10	3-11		3-16	
15			3-17	
20	3-12		3-18	
25			3-19	
30	3-13		3-20	
35	3-14		3-21	
40				
45	3-15			
50				
55				

Table 3 (cont.)

5	Compound No.	Q	Compound No.	Q
10	3-22		3-28	
15	3-23		3-29	
20	3-24		3-30	
25	3-25		3-31	
30	3-26		3-32	
35	3-27		3-33	
40			3-34	
45				
50				
55				

Table 3 (cont.)

5 Compound No.	Q	Compound No.	Q
10 3-35			
15 3-36			
20 3-37			
25 3-38			
30 3-39			
35 3-40			
40 3-41			
45 3-42			
50 3-43			
55 3-44			

Table 4

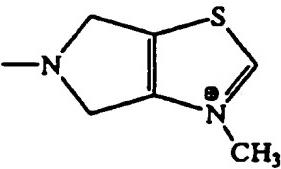
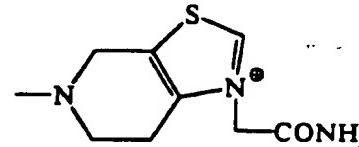
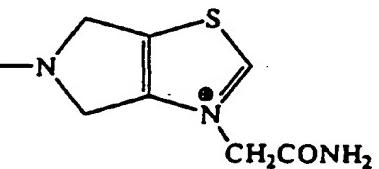
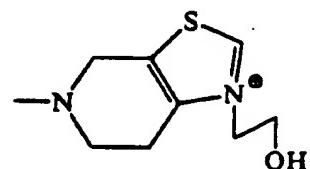
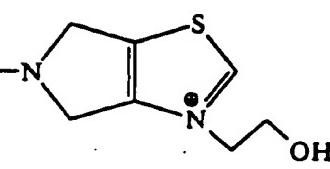
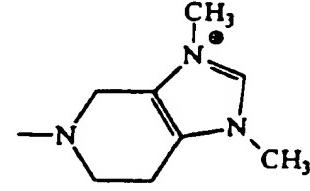
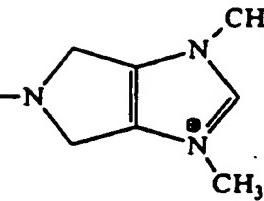
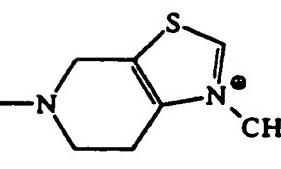
5	Compound No.	Q	Compound No.	Q
10	4-1		4-6	
15	4-2		4-7	
20	4-3		4-8	
25	4-4			
30	4-5			
35				
40				
45				
50				
55				

Table 5

5 Compound No.	Q	Compound No.	Q
10 5-1			
15 5-2			
20 5-3			
25 5-4			
30 5-5			
35 5-6			
40 5-7			
45 5-8			
50 5-9			
55 5-10			

Table 6

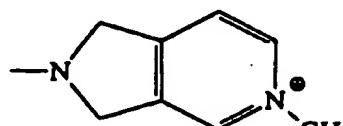
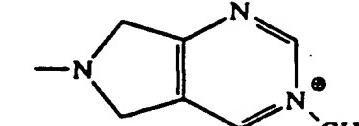
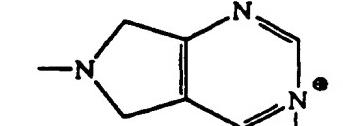
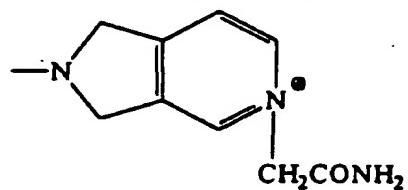
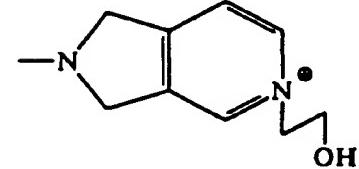
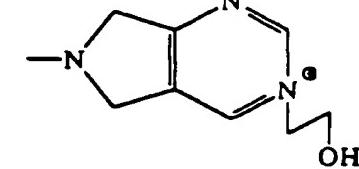
Compound No.	Q	Compound No.	Q
10	6-1 	6-4 	
15		6-5 	
20	6-2 		
25	6-3 	6-6 	
30			
35			
40			
45			
50			
55			

Table 7

Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	CH ₃		7-8	CH ₃	
15	CH ₃		7-9	CH ₃	
20	CH ₃		7-10	CH ₃	
25	CH ₃		7-11	CH ₃	
30	CH ₃		7-12	CH ₃	
35	CH ₃		7-13	CH ₃	
40	CH ₃		7-14	CH ₃	
45					
50					
55					

Table 7 (cont.)

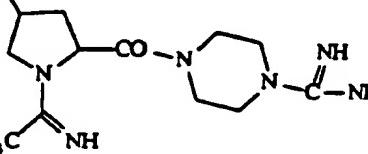
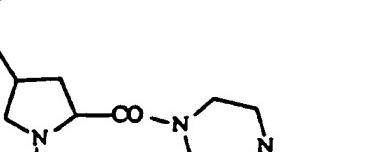
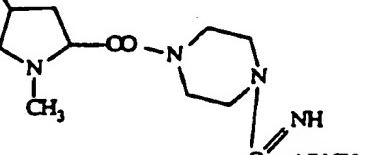
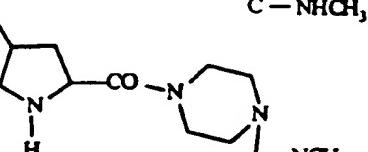
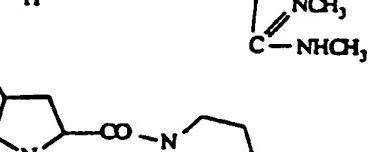
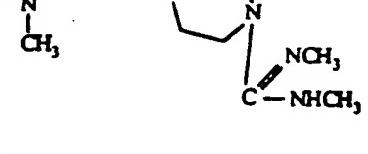
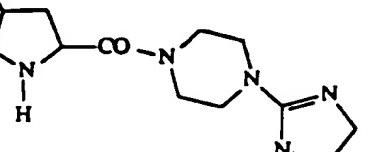
Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	7-15	CH ₃ 	7-21	CH ₃ 	
15	7-16	CH ₃ 	7-22	CH ₃ 	
20	7-17	CH ₃ 	7-23	CH ₃ 	
25	7-18	CH ₃ 	7-24	CH ₃ 	
30	7-19	CH ₃ 	7-25	H 	
35	7-20	CH ₃ 	7-26	H 	
40					
45					
50					
55					

Table 7 (cont.)

Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
7-27	H		7-33	CH ₃	
7-28	H		7-34	CH ₃	
7-29	H		7-35	CH ₃	
7-30	H		7-36	CH ₃	
7-31	H		7-37	H	
7-32	CH ₃		7-38	H	

Table 7 (cont.)

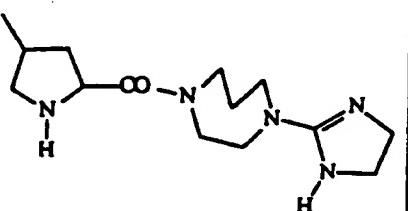
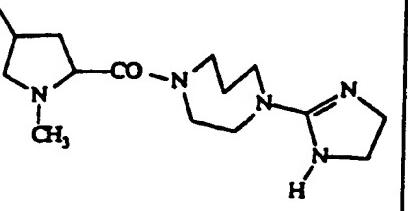
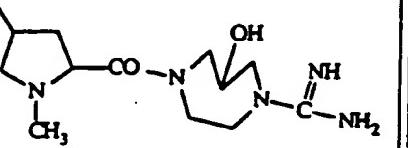
Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
5					
10	H				
15					
20	H				
25					
30	CH ₃				
35					
40					
45					
50					
55					

Table 8

5	Cpd. No.	R ¹	Het	Opd. No.	R ¹	Het
10	8-1	CH ₃		8-6	CH ₃	
15	8-2	CH ₃		8-7	CH ₃	
20	8-3	CH ₃		8-8	CH ₃	
25	8-4	CH ₃		8-9	CH ₃	
30	8-5	CH ₃		8-10	CH ₃	
35						
40						
45						
50						
55						

Table 8 (cont.)

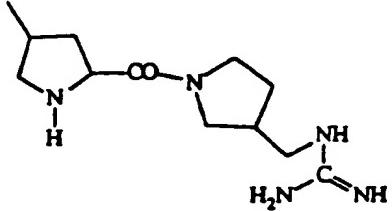
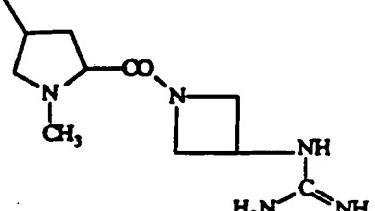
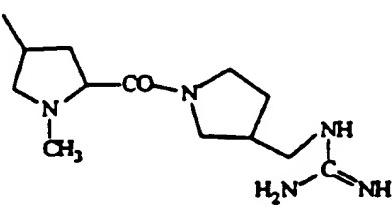
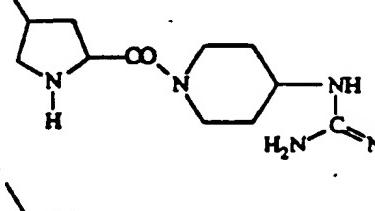
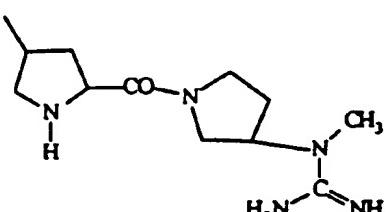
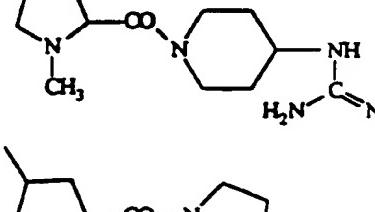
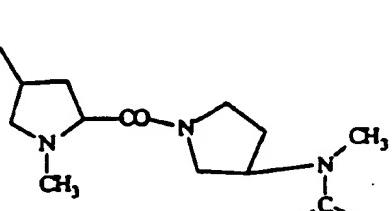
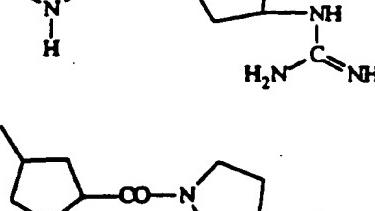
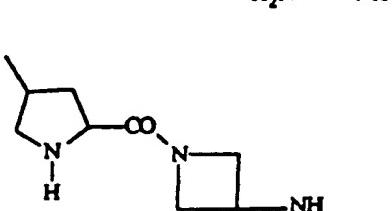
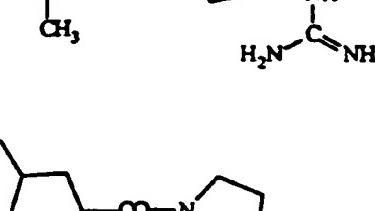
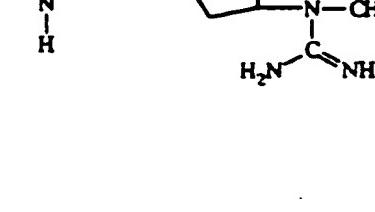
5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	8-11	CH ₃		8-16	CH ₃	
15	8-12	CH ₃		8-17	H	
20	8-13	CH ₃		8-18	H	
25	8-14	CH ₃		8-19	H	
30	8-15	CH ₃		8-20	H	
35				8-21	H	
40						
45						
50						
55						

Table 8 (cont.)

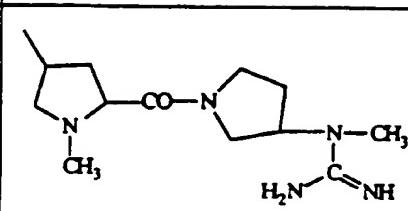
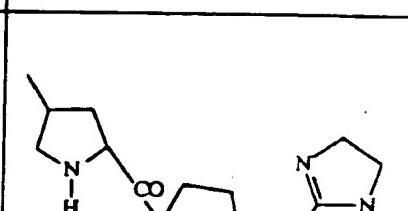
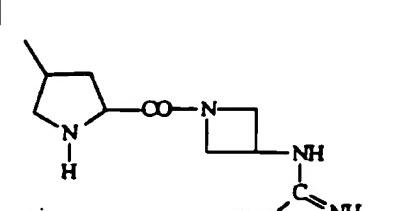
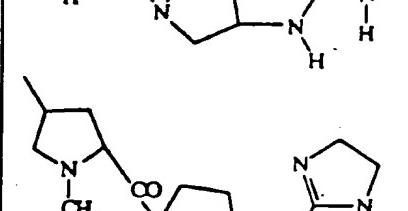
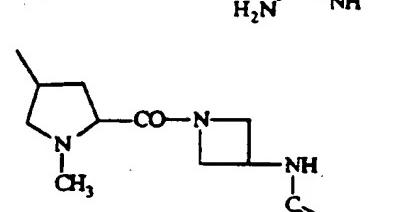
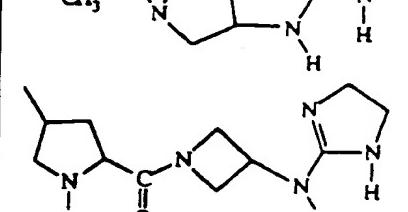
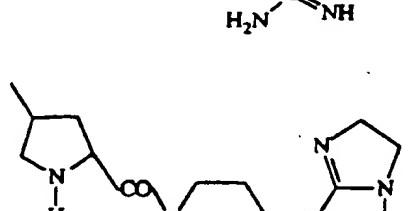
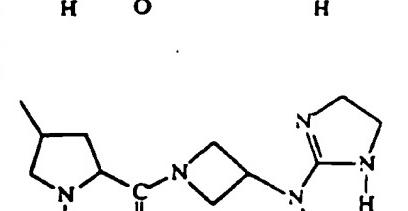
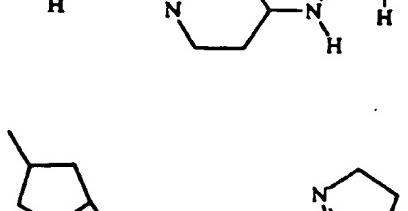
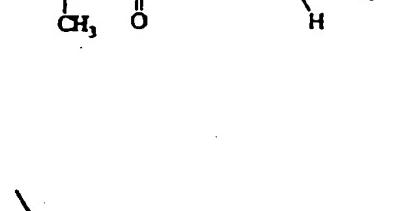
5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	8-22	H		8-27	CH ₃	
15	8-23	H		8-28	CH ₃	
20	8-24	H		8-29	CH ₃	
25	8-25	CH ₃		8-30	CH ₃	
30	8-26	CH ₃		8-31	CH ₃	
35						
40						
45						
50						
55						

Table 8 (cont.)

Table 9

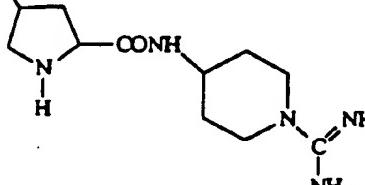
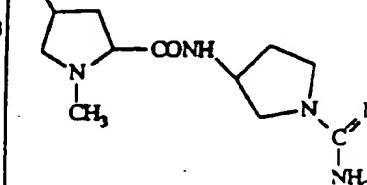
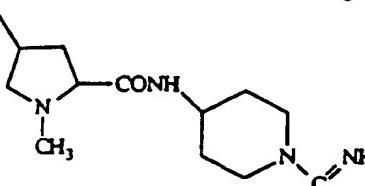
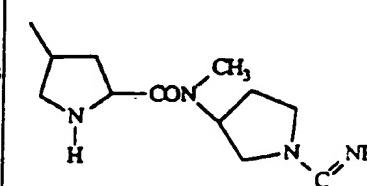
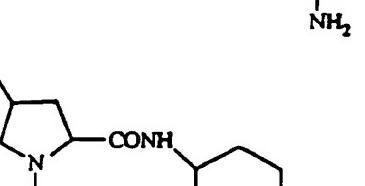
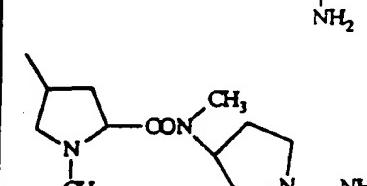
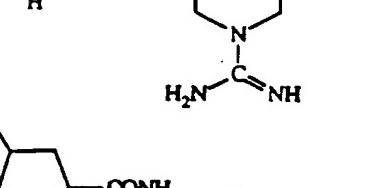
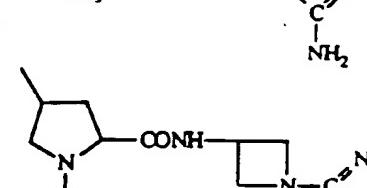
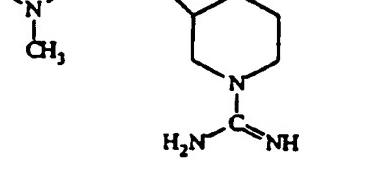
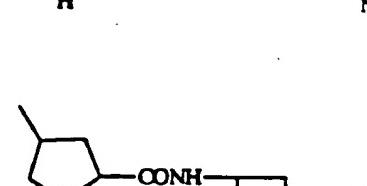
Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
9-1	CH ₃		9-6	CH ₃	
9-2	CH ₃		9-7	CH ₃	
9-3	CH ₃		9-8	CH ₃	
9-4	CH ₃		9-9	CH ₃	
9-5	CH ₃		9-10	CH ₃	

Table 9 (cont.)

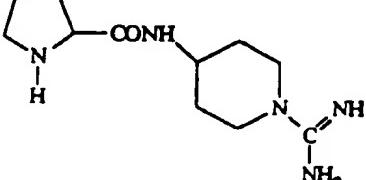
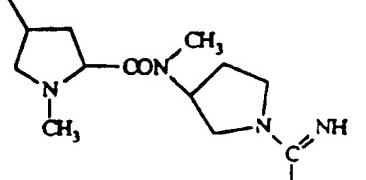
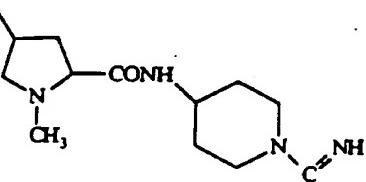
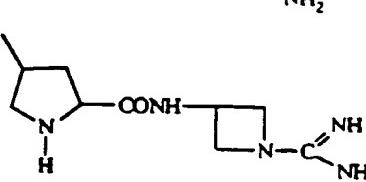
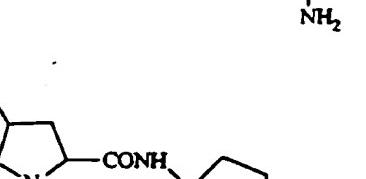
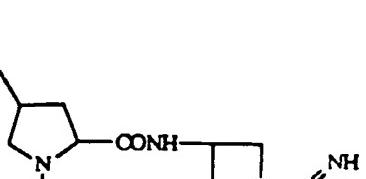
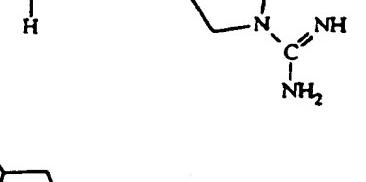
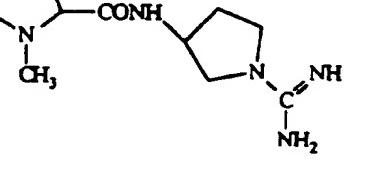
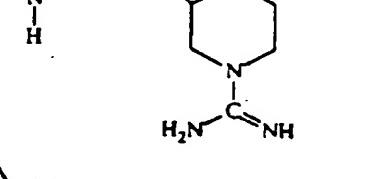
Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
9-11	H		9-16	H	
9-12	H		9-17	H	
9-13	H		9-18	H	
9-14	H		9-19	H	
9-15	H		9-20	H	

Table 10

5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	10-1	CH ₃		10-7	CH ₃	
15	10-2	CH ₃		10-8	CH ₃	
20	10-3	CH ₃		10-9	CH ₃	
25	10-4	CH ₃		10-10	CH ₃	
30	10-5	CH ₃		10-11	H	
35	10-6	CH ₃		10-12	H	
45						
50						
55						

Table 10 (cont.)

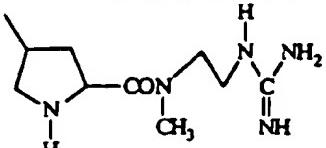
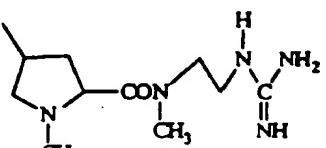
5	Cpd. No.	R ¹	Het		Cpd. No.	R ¹	Het
10	10-13	H					
15	10-14	H					
20							
25							
30							
35							
40							
45							
50							
55							

Table II

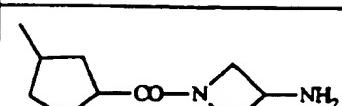
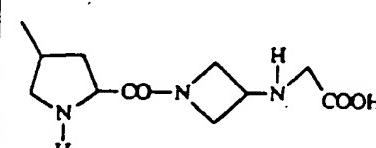
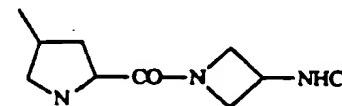
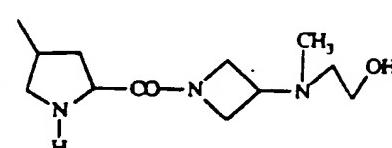
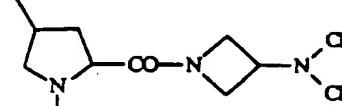
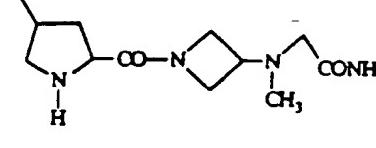
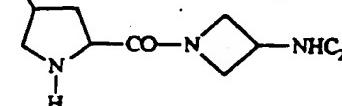
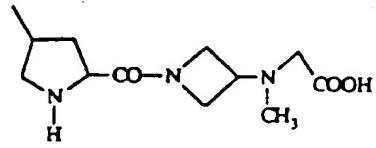
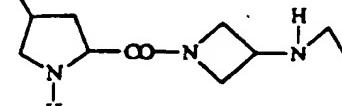
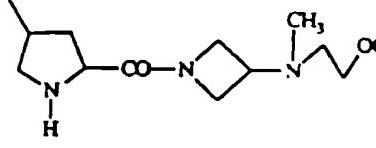
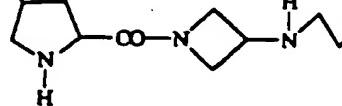
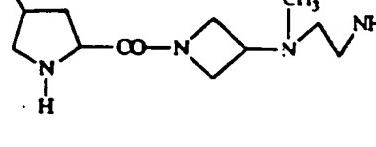
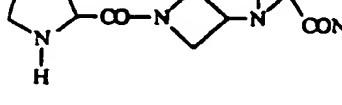
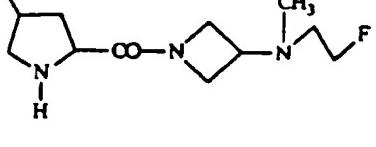
5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	11-1	CH ₃		11-8	CH ₃	
15	11-2	CH ₃		11-9	CH ₃	
20	11-3	CH ₃		11-10	CH ₃	
25	11-4	CH ₃		11-11	CH ₃	
30	11-5	CH ₃		11-12	CH ₃	
35	11-6	CH ₃		11-13	CH ₃	
40	11-7	CH ₃		11-14	CH ₃	
45						
50						
55						

Table II (cont.)

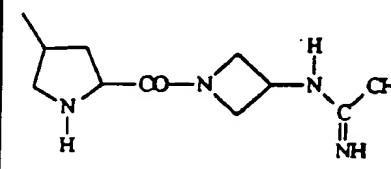
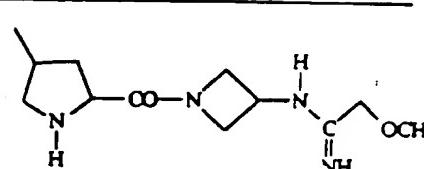
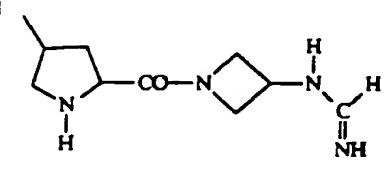
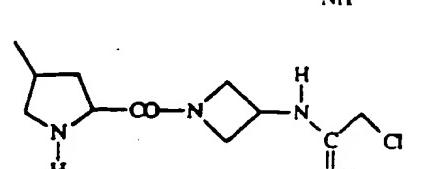
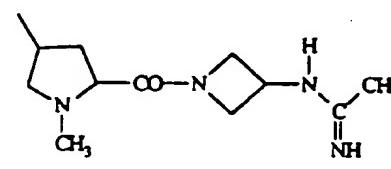
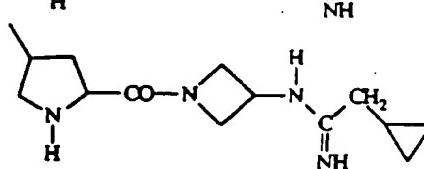
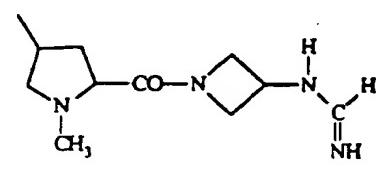
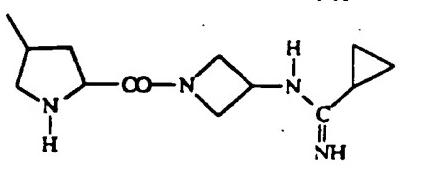
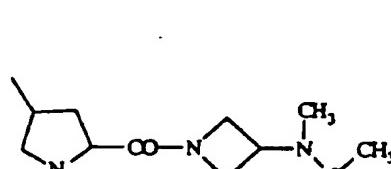
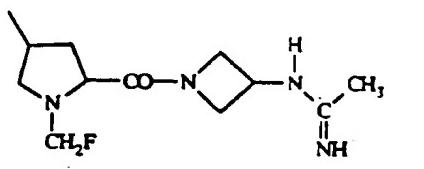
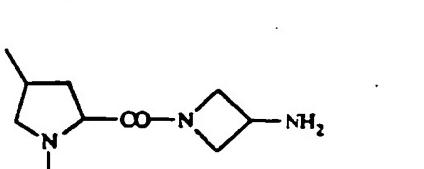
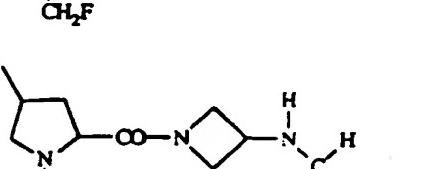
5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	11-15	CH ₃		11-21	CH ₃	
15	11-16	CH ₃		11-22	CH ₃	
20	11-17	CH ₃		11-23	CH ₃	
25	11-18	CH ₃		11-24	CH ₃	
30	11-19	CH ₃		11-25	CH ₃	
35	11-20	CH ₃		11-26	CH ₃	
40				11-27	CH ₃	
45						
50						
55						

Table II (cont.)

5	Cpd. No.	R ¹	Het		Cpd. No.	R ¹	Het
10	11-28	CH ₃			11-34	H	
15	11-29	CH ₃			11-35	H	
20	11-30	CH ₃			11-36	H	
25	11-31	CH ₃			11-37	H	
30	11-32	H			11-38	H	
35	11-33	H			11-39	H	
40							
45							
50							
55							

Table II (cont.)

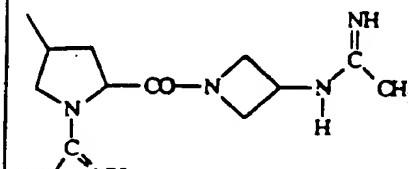
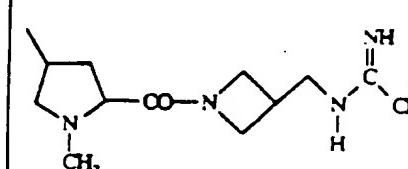
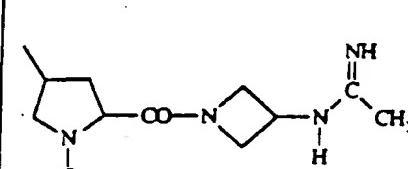
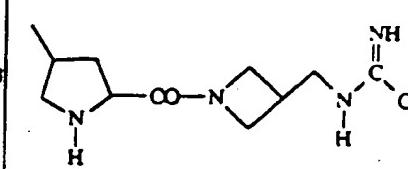
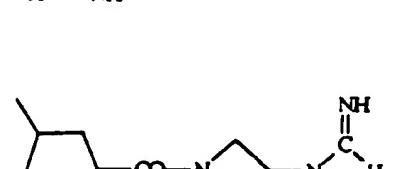
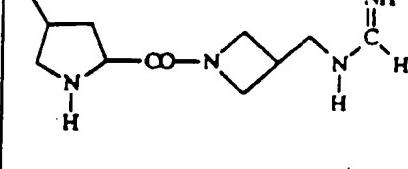
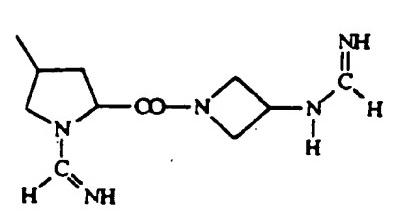
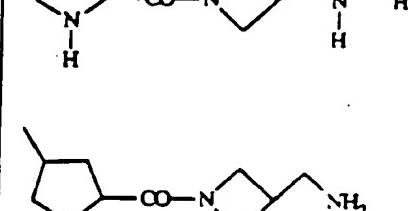
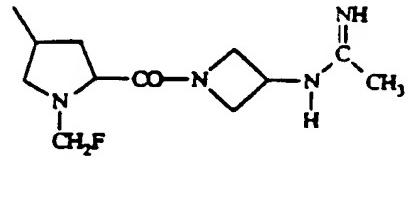
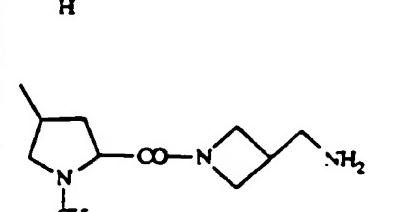
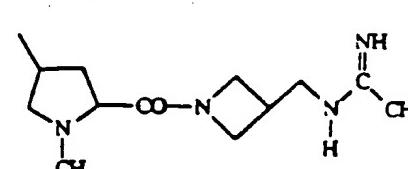
5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	11-40	H		11-45	H	
15	11-41	H		11-46	CH ₃	
20	11-42	H		11-47	CH ₃	
25	11-43	H		11-48	CH ₃	
30	11-44	H		11-49	CH ₃	
35				11-50	CH ₃	
40						
45						
50						
55						

Table II (cont.)

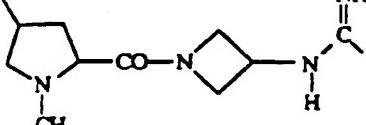
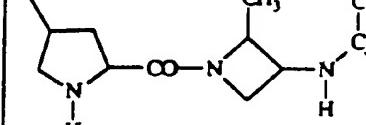
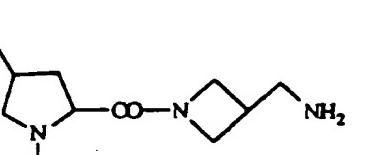
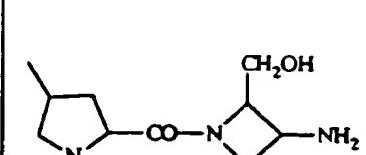
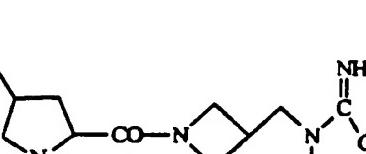
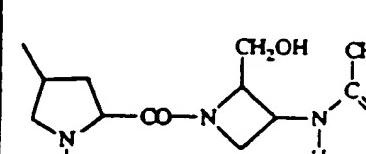
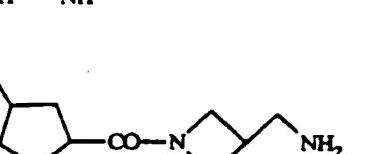
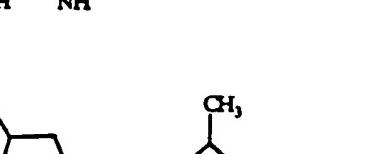
5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	11-51	CH ₃		11-56	CH ₃	
15	11-52	CH ₃		11-57	CH ₃	
20	11-53	CH ₃		11-58	CH ₃	
25	11-54	CH ₃				
30	11-55	CH ₃				
35						
40						
45						
50						
55						

Table 12

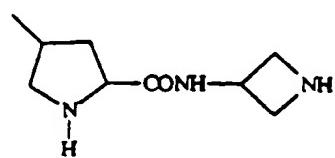
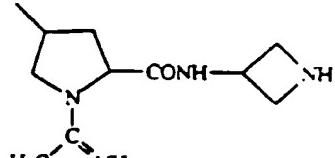
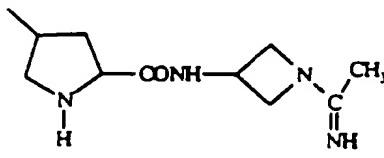
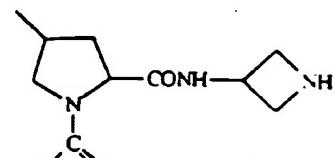
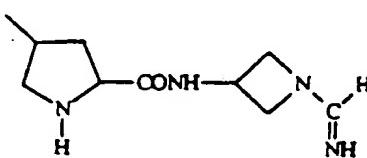
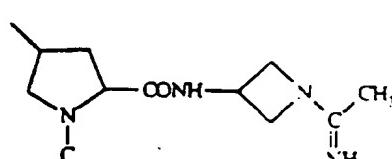
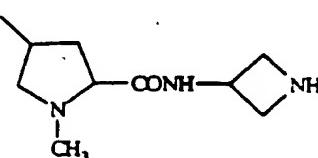
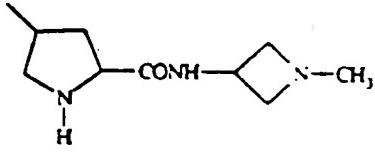
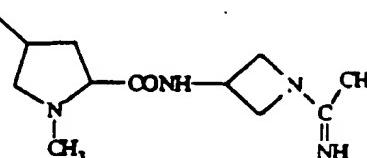
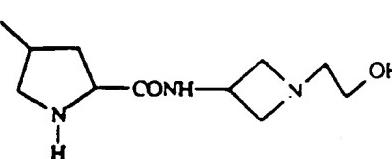
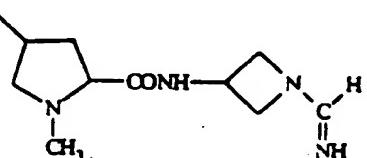
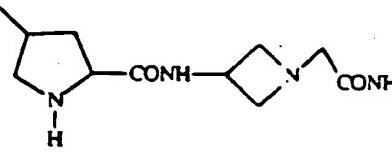
	Cpd. No.	R ¹	Het		Cpd. No.	R ¹	Het
5							
10	12-1	CH ₃			12-7	CH ₃	
15	12-2	CH ₃			12-8	CH ₃	
20	12-3	CH ₃			12-9	CH ₃	
25	12-4	CH ₃			12-10	CH ₃	
30	12-5	CH ₃			12-11	CH ₃	
35	12-6	CH ₃			12-12	CH ₃	
40							
45							
50							
55							

Table 12 (cont.)

Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	CH ₃		12-19	CH ₃	
15	CH ₃		12-20	CH ₃	
20	CH ₃		12-21	CH ₃	
25	CH ₃		12-22	CH ₃	
30	CH ₃		12-23	H	
35	CH ₃		12-24	H	
40					
45					
50					
55					

Table 12 (cont.)

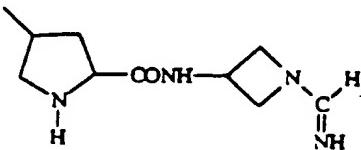
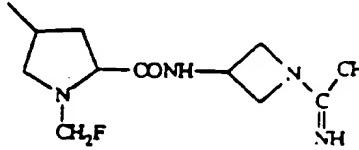
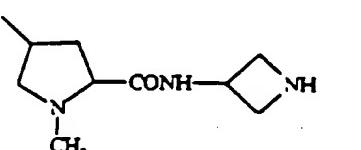
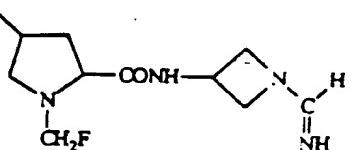
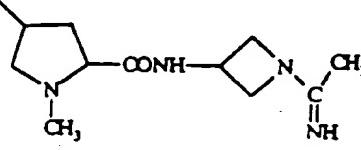
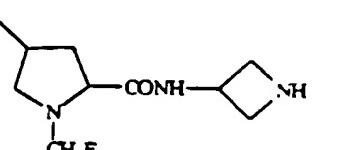
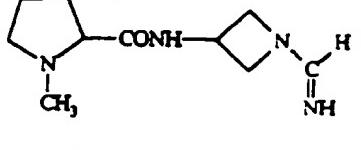
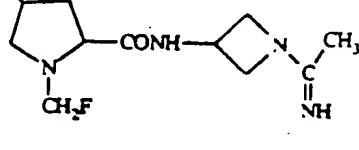
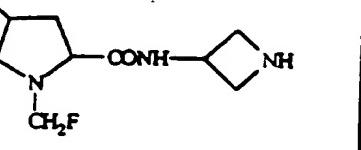
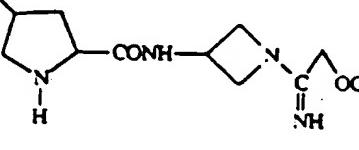
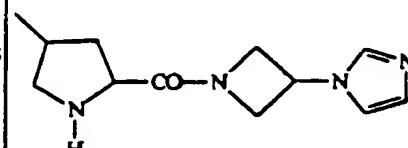
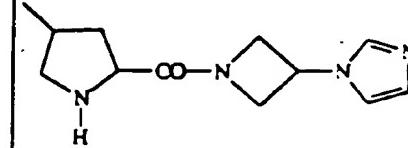
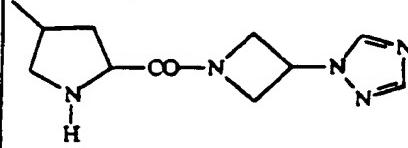
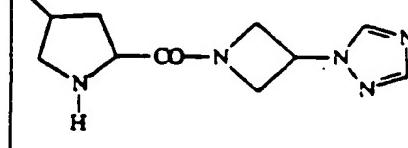
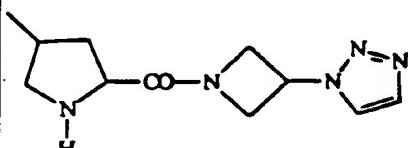
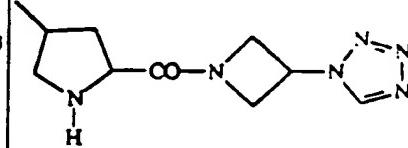
Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
12-25	H		12-30	CH ₃	
12-26	H		12-31	CH ₃	
12-27	H		12-32	H	
12-28	H		12-33	H	
12-29	CH ₃		12-34	CH ₃	

Table 12 (cont.)

5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	12-35	CH ₃				
15	12-36	CH ₃				
20	12-37	CH ₃				
25	12-38	CH ₃				
30						
35						
40						
45						
50						
55						

Table 13

5	Cpd. No.	R ¹	Het	Cpd. No.	R ¹	Het
10	13-1	CH ₃		13-4	H	
15	13-2	CH ₃		13-5	H	
20	13-1	CH ₃		13-6	CH ₃	
25						
30						
35						
40						
45						
50						
55						

Of the specific compounds of the present invention, preferred compounds are:

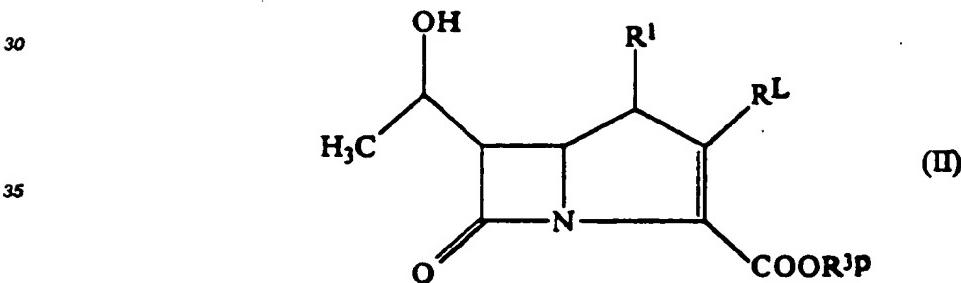
- 6-(1-Hydroxyethyl)-1-methyl-2-[2-(3-trimethylammonio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 - 5 2-[2-(1,1-Dimethyl-3-pyrrolidinoaminocarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
 - 2-[2-[3-(Carbamoylmethyl)dimethylammonio]pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
 - 10 2-[2-[3-(2-Hydroxyethyl)dimethylammonio]pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
 - 2-[2-(3-[N-(2-Fluoroethyl)-N,N-dimethylammonio]pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
 - 15 6-(1-Hydroxyethyl)-1-methyl-2-[2-[4-(3-methylimidazolio)piperidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 - 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(3-methylimidazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 - 20 2-[2-(4-Amidinopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 - 2-[2-(4-Amidinopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 - 25 2-[2-(4-Amidinohomopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 - 2-[2-(3-Aminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 - 30 2-[2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 - 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(4-methyl-1,2,4-triazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 - 35 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(4-methyl-1,2,4-triazolio)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 - 6-(1-Hydroxyethyl)-1-methyl-2-[2-(3-trimethylammonioazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 - 40 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(2-Fluoroethyl)-1-imidazolio]azetidin-1-yl-carbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
 - 2-[2-(3-[2-Fluoroethyl]dimethylammonio)azetidin-1-yl-carbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
 - 45 2-[2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
- and pharmaceutically acceptable salts thereof.

The most preferred compounds are:

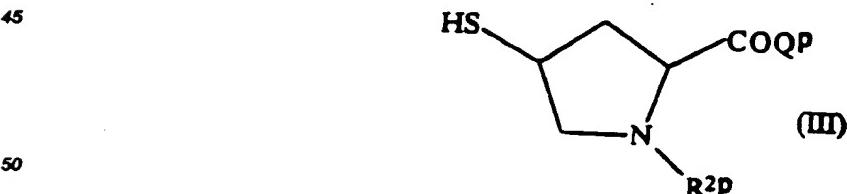
- 6-(1-Hydroxyethyl)-1-methyl-2-[2-(3-trimethylammonio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
- 50 2-[2-(3-Carbamoylmethyl)dimethylammonio]pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
- 2-[2-(3-[2-Hydroxyethyl]dimethylammonio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
- 55 2-[2-(3-[N-(2-Fluoroethyl)-N,N-dimethylammonio]pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate;
- 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(3-methylimidazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
- 2-[2-(4-Amidinopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-car-

boxylic acid;
 2-[2-(4-Amidinopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 2-[2-(4-Amidinohomopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 5 2-[2-(4-Amidinohomopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 2-[2-(4-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 10 2-[2-(3-Formimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 2-[2-(3-Aminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 15 2-[2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid;
 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(4-methyl-1-1,2,4-triazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(4-methyl-1-1,2,4-triazolio)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 20 6-(1-Hydroxyethyl)-1-methyl-2-[2-(3-trimethylammonioazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 6-(1-Hydroxyethyl)-1-methyl-2-[2-[3-(3-methyl-1-imidazolio)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate;
 and pharmaceutically acceptable salts thereof.

25 The compounds of the present invention may be prepared by a variety of processes well known in the art for the preparation of compounds of this type. For example, in general terms, they may be prepared by reacting a carbapenem compound of formula (II):



40 (in which R¹ is as defined above, R^L represents a sulphonyloxy or phosphoryloxy group or a group of formula -S(O)R^{L1}, R^{L1} represents an alkyl group, a haloalkyl group, an alkanoylaminoalkyl group, an alkenoylaminoalkyl group, an aryl group or an aromatic heterocyclic group, and R^{3P} represents a carboxy-protecting group) with a pyrrolidine derivative of formula (III):



55 (in which R^{2P} represents any of the groups or atoms represented by R² or any such group or atom which has been protected, and Q^P represents any of the groups or atoms represented by Q or any such group or atom which has been protected or any such group in which a quaternary nitrogen atom is replaced by a corresponding tertiary nitrogen atom, and, where the group Q^P contains a quaternary nitrogen atom, the compound is accompanied by a balancing anion),
 and, if necessary, converting any non-quaternized nitrogen atom to the corresponding quaternary nitrogen in

the group f formula (Q-I), (Q-II), (Q-IV), (Q-V) or (Q-VI) or in the group represented by Z, and, if necessary, removing any protecting groups, and optionally sialifying and/or esterifying the product.

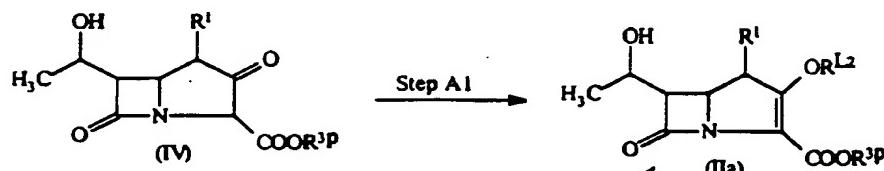
In more detail, the reactions involved may be as illustrated in the following Reaction Schemes A and B:

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Reaction Scheme A:

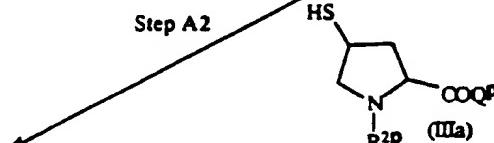
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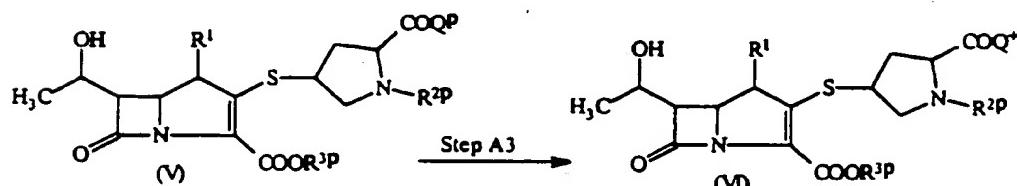
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Step A2

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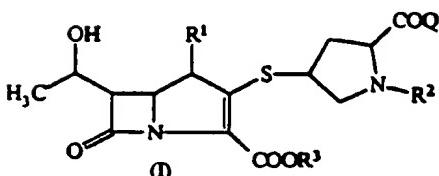
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Step A5

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Step A4

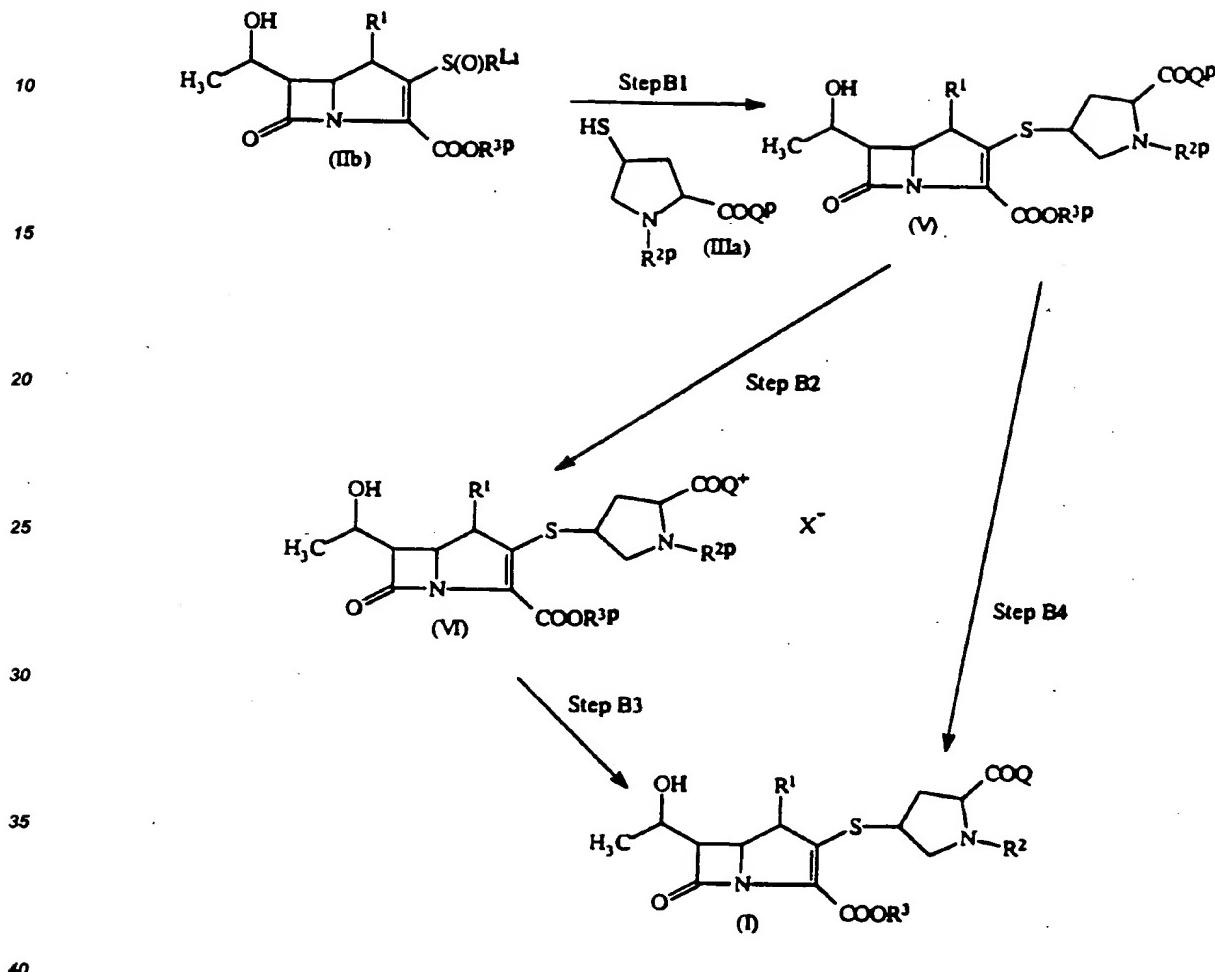
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Reaction Scheme B:

In the above formulae, R¹, R², R³, R^{2p}, R^{3p}, QP and Q are as defined above.

R¹ represents:

- 45 an alkyl group, such as a methyl, ethyl, propyl or isopropyl group;
- a haloalkyl group, such as a fluoromethyl, chloromethyl, fluoroethyl, chloroethyl, fluoropropyl, difluoromethyl, difluoroethyl, dichloroethyl, trifluoromethyl or trifluoroethyl group;
- a 2-acetamidoethyl group;
- a 2-acetamidovinyl group;
- 50 an optionally substituted aryl group, such as a phenyl or naphthyl group which may be unsubstituted or may have from 1 to 3 substituents which may be the same or different from one another, for example: fluorine, chlorine, bromine, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, nitro, carbamoyl, mono- and di-substituted alkylcarbamoyl (where the alkyl group is, for example, methyl, ethyl or propyl), hydroxy or cyan ;
- 55 or an optionally substituted aromatic heterocyclic group, such as a pyridyl and pyrimidyl group, which may be unsubstituted or may have from 1 to 3 substituents which may be the same or different from one another, for example: fluorin , chlorin , bromin , methyl, ethyl, propyl and isopropyl.

R² represents:

an alkanesulphonyl group, such as a methanesulphonyl, trifluoromethanesulphonyl, ethanesulphonyl, propane-sulphonyl, isopropanesulphonyl or butanesulphonyl group;

an arylsulphonyl group, such as a phenylsulphonyl, tolylsulphonyl, e.g. *p*-tolylsulph nyl, or 1- or 2-naphthylsulph nyl group;

5 a dialkylphosphoryl group, such as a dimethylphosphoryl, diethylphosphoryl, dipropylphosphoryl, diisopropylphosphoryl, dibutylphosphoryl or dipentylphosphoryl group;

or a diarylphosphoryl group, such as a diphenylphosphoryl or ditolylphosphoryl group.

Q^+ represents any of the groups represented by Q which includes a quaternary nitrogen atom.

10 X⁻ represents an anion, for example a chlorine atom, a bromine atom, an iodine atom, a monomethyl sulphate group, a sulphate group, a methanesulphonyloxy group, a toluenesulphonyloxy group, a trifluoromethanesulphonyloxy group or a fluorosulphonyloxy group.

If Q^p or R^{3p} includes a protecting group, this may be selected from the many such groups well known to those skilled in the art and commonly used for the protection of hydroxy groups, imino groups, amino groups or carboxy groups. Such groups are described fully in many standard texts, for example T.W. Greene, "Protective Groups in Organic Synthesis", published by John Wiley & Son. Examples of such groups typically include the *p*-nitrobenzyloxycarbonyl and *p*-nitrobenzyl groups.

15 As defined above, R^{3p} represents a protecting group for the carboxy group, such as an alkyl group, e.g. a methyl, ethyl or t-butyl group; an aralkyl group, e.g. a benzyl, diphenylmethyl, 4-nitrobenzyl or 2-nitrobenzyl group; an alkenyl group, e.g. an allyl, 2-chloroallyl or 2-methylallyl group; a haloalkyl group, e.g. a 2,2,2-trichloroethyl, 2,2-dibromoethyl or 2,2,2-tribromoethyl group; or a 2-trimethylsilylethyl group.

20 In Step A1 of Reaction Scheme A, a carbapenam compound of formula (IV) is converted to a carbapenem-compound of formula (IIa) by reaction with an active sulphonyl or phosphoryl compound containing a group corresponding to the group R¹², for example an alkanesulphonic anhydride, an arylsulphonic anhydride, a dialkylphosphoryl halide or a diarylphosphoryl halide.

25 This reaction is normally and preferably effected in the presence of a base. There is no particular restriction on the nature of the base employed, provided that it has no adverse effect on other parts of the molecule, notably the β -lactam ring, and preferred examples include organic bases such as triethylamine, diisopropylethylamine and 4-dimethylaminopyridine.

30 Examples of sulphonyl or phosphoryl compounds which may be employed in this reaction include: alkanesulphonic anhydrides, such as methanesulphonic anhydride, trifluoromethanesulphonic anhydride and ethanesulphonic anhydride; arylsulphonic anhydrides, such as benzene-sulphonic anhydride and *p*-toluenesulphonic anhydride; dialkylphosphoryl halides, such as dimethylphosphoryl chloride and diethylphosphoryl chloride; and diaryl-phosphoryl halides, such as diphenylphosphoryl chloride and diphenylphosphoryl bromide. Of these reagents, we particularly prefer *p*-toluenesulphonic anhydride and diphenylphosphoryl chloride.

35 The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as methylene chloride, 1,2-dichloroethane and chloroform; nitriles, such as acetonitrile; and amides, such as dimethylformamide and dimethylacetamide.

40 The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a relatively low temperature, for example from -20°C to 40°C, in order to suppress any side reactions. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 5 hours will usually suffice.

45 The compound of formula (IIa) thus obtained is not normally isolated; instead, in Step A2, the reaction mixture is reacted, without any isolation, with a mercaptan of formula (IIIa) in the presence of a base to obtain a compound of formula (V). The resulting compound may then, if necessary, be subjected, in Step A5, to a de-protection reaction to eliminate any protecting group in the groups represented by R^{3p} or Q^p and thus to prepare the desired compound of formula (I).

50 There is no particular limitation on the nature of the base which may be employed in Step A2, provided that it has no adverse effect on other parts of the molecule, notably the β -lactam ring, and preferred examples include: organic bases, such as triethylamin and diisopropylethylamine; and inorganic bases, such as potassium carbonate and sodium carbonate. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature from -20°C to room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined

above, a period of from 30 minutes to 5 days will usually suffice.

After completion of the reaction, the desired compound of formula (V) can be collected from the reaction mixture by any conventional procedure. For example, in one suitable recovery procedure, the solvent is removed from the reaction mixture by distillation to obtain the desired compound. Alternatively, in the case of the non-quaternary compounds, the solvent is removed, preferably by evaporation, the residue is extracted with an organic solvent, and the extract is washed with water and dried, after which the solvent is removed by evaporation. The compound thus obtained can be further purified, if necessary, by conventional procedures, such as recrystallisation, reprecipitation or the various chromatography techniques, notably column chromatography. If desired, the compound can be purified by subjecting the reaction mixture directly to reprecipitation. Alternatively, if desired, the compound of formula (V) can be subjected to the subsequent carboxy deprotection reaction in Step A5 without isolation.

If necessary, in Step A5, the compound of formula (V) obtained in Step A2 can be converted to a carboxylic acid derivative of formula (I) by eliminating the protecting group R^{3p} for the carboxy group by conventional means. The nature of the reaction employed for the elimination of the protecting group will, of course, vary, depending upon the nature of the protecting group, as is well known in the art. For example, where the protecting group can be eliminated by reduction (as can the haloalkyl groups, the aralkyl groups, and the benzhydryl group), this can be achieved by bringing the compound of formula (V) into contact with a reducing agent. Examples of preferred reducing agents which may be employed in this reaction include: zinc and acetic acid when the carboxy-protecting group is, for example, a haloalkyl group (such as a 2,2-dibromoethyl or 2,2,2-trichloroethyl group); or, when the protecting group is, for example, an aralkyl group (such as a benzyl or 4-nitrobenzyl group) or a benzhydryl group, it is possible to use as the reducing agent either an alkali metal-sulphide (such as sodium sulphide or potassium sulphide) or hydrogen in the presence of a reducing catalyst (such as palladium-on-carbon). The reducing reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: alcohols, such as methanol or ethanol; ethers, such as tetrahydrofuran or dioxan; fatty acids, such as acetic acid; and mixtures of any one or more of such organic solvents with water. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0°C to approximately room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 12 hours will usually suffice.

If Q^p and/or R^{2p} includes a protecting group for a hydroxy group, an imino group, an amino group or a carboxy group (for example a p-nitrobenzyloxycarbonyl group or a p-nitrobenzyl group), such a protecting group can be eliminated simultaneously with the elimination of the above-mentioned carboxy-protecting group (in the case where R^{3p} is a p-nitrobenzyl group).

After completion of the reaction, the desired compound of the present invention can be collected from the reaction mixture by conventional means. For example, one suitable recovery procedure comprises: removing insolubles precipitated from the reaction mixture by filtration; and then removing the solvent by distillation. The compound thus obtained can be further purified, if necessary, by conventional procedures, such as recrystallisation, reprecipitation or the various chromatography techniques, notably column chromatography.

Alternatively, where Q represents one of the groups containing a quaternary nitrogen atom, it may be prepared from a mercaptan of formula (IIIa) in which Q^p represents a corresponding tertiary nitrogen atom. In this case, in Step A2, the compound of formula (IIa) is reacted with such a mercaptan of formula (IIIa), to give a compound of formula (V). This is then converted to a corresponding quaternary ammonium compound in Step A3, and then, if necessary, deprotected in Step A4, to give the desired compound of formula (I).

Quaternisation in Step A3 can be carried out using methods well known in the art, for example by reacting the compound of formula (V) with a compound of formula RX, in which R represents an optionally substituted alkyl group, which may be as defined above in relation to any of the groups attached to a quaternary nitrogen atom in the groups represented by Q or Z. X represents a halogen atom (for example a chlorine atom, a bromine atom or an iodine atom), a monomethyl sulphate group, a sulphate group, or a sulphonyloxy group (for example a methanesulphonyloxy, toluen sulphonyloxy, trifluoromethan sulphonyloxy or fluorosulphonyloxy group). In the reaction for converting the nitrogen atom into a quaternary atom, the compounds of formulae (V) and RX may be reacted directly, or a solvent may be used. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as methylene chloride, 1,2-dichloroethane or chloroform; nitriles, such as acetonitrile; ethers,

such as tetrahydrofuran; esters, such as ethyl acetate; and amides, such as dimethylformamide or dimethylacetamide. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -20°C to 100°C.

- 5 After completion of the reaction, the desired compound of formula (VI) can be collected from the reaction mixture by conventional means. For example, the solvent in the reaction mixture is simply evaporated off. The compound thus obtained can be further purified, if necessary, by conventional procedures, such as recrystallisation, reprecipitation or the various chromatography techniques, notably column chromatography. Alternatively, the desired compound can be purified by subjecting the reaction mixture to precipitation. If required, 10 the compound of formula (VI) can be subjected, in Step A4, to the subsequent step of carboxy deprotection without isolation, which may be carried out as described above in relation to Step A5.

- 15 The carboxy group of the compound thus obtained can be converted to an ester group, particularly to such a group which undergoes hydrolysis under physiological conditions, by conventional means. When R³ is an ester which undergoes hydrolysis under physiological conditions [such as an alkanoyloxyalkyl group, e.g. a pivaloyloxyethyl or acetoxyethyl group, an alkoxy carbonyloxyalkyl group, e.g. a 1-(ethoxycarbonyloxy)ethyl or 1-(isopropoxycarbonyloxy)ethyl group, or a phthalidyl, indanyl, methoxymethyl or 2-oxo-5-methyl-1,3-dioxolen-4-ylmethyl group], the compound of formula (I) need not be deprotected and can be administered directly to a patient, since such a compound can be hydrolyzed in a living body under physiological conditions.

- 20 Alternatively, the compound (V) can be prepared, as shown in Reaction Scheme B, from a compound (IIb). This compound of formula (IIb) can be synthesized by the method disclosed in Japanese Unexamined Patent Publication No. Sho-62-30781 (Kokai). The reaction of the compound of formula (IIb) with a mercaptan of formula (IIIa) in the presence of a base to give a compound of formula (V) is normally and preferably carried out in an inert solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: tetrahydrofuran, acetonitrile, dimethylformamide, dimethyl sulphoxide, water and mixtures of any two or more of these solvents. There is also no particular limitation on the nature of the base employed, provided that it does not affect other portions of the compound, particularly the β-lactam ring, and examples include: organic bases, such as diisopropylethylamine, triethylamine, N-methylpiperidine or 4-dimethylaminopyridine; and inorganic bases, such as potassium carbonate or sodium hydrogen carbonate. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a relatively low temperature in order to suppress any side reaction, usually at a temperature of from -20°C to 40°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 5 minutes to 5 days will usually suffice.

25 After completion of the reaction, the desired compound of formula (V) can be collected from the reaction mixture by conventional means, as described in relation to Reaction Scheme A. It may then be subjected to Step B2 and B3 or Step B4, which correspond to Steps A3 and A4 or A5 of Reaction Scheme A.

- 30 40 Any of the compounds prepared as described above may be saponified and/or esterified by conventional means well known in the art.

45 The compounds of the present invention exhibit excellent antibacterial activity with a broad antibacterial spectrum, and have the ability to inhibit the activity of β-lactamase, unlike most thienamycin-type compounds, which are liable to be metabolised in the mammalian body. The derivatives of the present invention, in addition, exhibit excellent stability against dehydropeptidase I, which is also known to catalyse the inactivation of compounds of the thienamycin type. The derivatives of the present invention showed a strong antibacterial activity against a wide range of pathogenic bacteria including Gram-positive bacteria such as Staphylococcus aureus, and Enterococcus faecalis, Gram-negative bacteria such as Escherichia coli, Shigella species, Streptococcus pneumoniae, Proteus species, Serratia species, Enterobacter species and Pseudomonas species, and anaerobic bacteria such as Bacteroides fragilis.

50 55 The antibacterial activity was determined by the agar plate dilution method, and the minimal inhibitory concentrations of the compounds of the present invention against a variety of common pathogenic bacteria were determined and are shown in the following Table 14. In the Table, the compounds of the present invention are identified by reference to one of the following Examples which illustrates its preparation.

The microorganisms used are identified as follows:

A:Staphylococcus aureus 209P;

B:Escherichia coli NIHJ;

C:Pseudomonas aeruginosa 1001.

Tabl 14

	Compound of Example No.	Microorganism		
		A	B	C
5	11	0.02	0.02	0.2
10	12	≤0.01	≤0.01	0.1
15	35	≤0.01	≤0.01	0.1
20	36	≤0.01	≤0.01	0.1
25	43	≤0.01	≤0.01	0.1
30	Imipenem	≤0.01	0.05	3.1

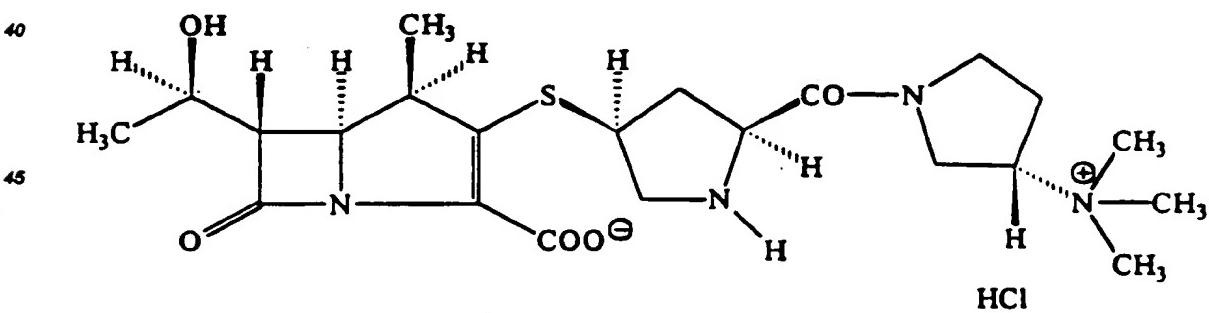
These results demonstrate that the compounds of the present invention have activities which are, in general, better than that of imipenem; moreover, they are, unlike imipenem, resistant to dehydropeptidase I and β -lactamase.

The carbapenem-3-carboxylic acid derivatives of the present invention, therefore, are useful as therapeutic agents for the treatment and prophylaxis of infections caused by these pathogenic bacteria. The compounds may be administered in any conventional form for this purpose, and the exact formulation used will depend on the disease to be treated, the age and condition of the patient and other factors, which are well known in the art. For example, for oral administration, the compounds may be formulated as tablets, capsules, granules, powders or syrups; and for parenteral administration, they may be formulated for intravenous injection or intramuscular injection. The dosage will vary widely, depending upon the age, body weight, symptoms and condition of the patient, as well as the mode of administration and times and routine of administration; however, for an adult human patient, a daily dosage of from about 100 mg to 3000 mg is recommended, and this may be administered as a single dose or in divided doses.

The preparation of certain of the compounds of the invention is further illustrated by the following Examples, and the preparation of certain starting materials is illustrated by the subsequent Preparations. All mesh sizes used herein are Tyler standard mesh.

EXAMPLE 1

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-((2S,4S)-2-[(3S)-3-trimethylammoniopyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio)-1-carbapen-2-em-3-carboxylate hydrochloride



1(1) (2S,4S)-2-[(3S)-3-Dimethylamino-1-pyrrolidinylicarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxy-carbonyl)pyrrolidine

924 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 10 ml of dry tetrahydrofuran, and the resulting solution was cooled to -20°C. 209 mg of triethylamin, followed by 250 mg of pivaloyl chloride, were then added to the solution, after which the mixture was stirred at the same temperature for 5 minutes. At the end of this time, a mixture of 651 mg of (3S)-3-di-

methylaminopyrrolidine trifluoroacetate, 560 mg of diisopropylethylamine and 7 ml of dry acetonitrile was added to the mixture, and the mixture was gradually heated and then stirred at 0°C for 1 hour. After this, the reaction mixture was filtered, and the solvent was removed by evaporation under reduced pressure. The resulting residue was diluted with ethyl acetate, and the diluted solution was washed with an aqueous solution of sodium

5 hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 3 : 1 by volume mixture of acetonitrile and methanol as the eluent, to obtain 884 mg of the title compound as a powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

10 1710, 1654, 1512, 1345, 1109, 857, 738.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

14.9 - 3.31 (15H, multiplet);

3.35 - 3.57 (2H, multiplet);

3.71 - 4.00 (6H, multiplet);

4.44 - 4.56 (1H, multiplet);

5.00 - 5.21 (2H, multiplet);

6.88 (2H, doublet, J = 8.79 Hz);

7.27 (2H, doublet, J = 8.31 Hz);

7.51 - 7.61 (2H, multiplet);

8.19 - 8.26 (2H, multiplet).

20

1(2) (2S,4S)-2-[(3S)-3-Dimethylamino-1-pyrrolidinylcarbonyl]-4-mercaptop-1-(4-nitrobenzylloxycarbonyl)-pyrrolidine trifluoromethanesulphonate

25 845 mg of (2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzylloxycarbonyl)pyrrolidine [prepared as described in step (1) above] were suspended in 1.7 ml of anisole, and 8.5 ml of trifluoroacetic acid and 0.28 ml of trifluoromethanesulphonic acid were added to the resulting suspension, whilst ice-cooling, after which the mixture was stirred at room temperature for 1 hour. The cycle comprising removing the solvent by evaporation under reduced pressure, washing the residue with hexane to remove anisole, adding diethyl ether to the mixture, cooling the mixture to -78°C to solidify the product and milling the product, followed by decantation, was repeated several times to obtain 1.14 g of the title compound as a powder.

30

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1705, 1656, 1523, 1348, 857.

35

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

1.70 - 4.10 (18H, multiplet);

4.47 - 4.66 (1H, multiplet);

5.04 - 5.27 (2H, multiplet);

7.51 - 7.65 (2H, multiplet).

40

1(3) 4-Nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzylloxycarbonyl)pyrrolidin-4-ythio]-1-carbapen-2-em-3-carboxylate

45 544 mg of 4-nitrobenzyl (1R,5R,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 5.4 ml of dry acetonitrile, and 424 mg of diphenyl phosphorylchloride and 204 mg of diisopropylethylamine were added dropwise to the resulting solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 1 hour. A solution of 582 mg of diisopropylethylamine and 1.10 g of (2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-4-mercaptop-1-(4-nitrobenzylloxycarbonyl)pyrrolidine trifluoromethanesulphonate [prepared as described in step (2) above] in 4 ml of dry acetonitrile was then added dropwise, whilst ice-cooling, to the mixture, after which the mixture was stirred at the same temperature for 6 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting residue was dissolved in methylene chloride and washed with water, with an aqueous solution of sodium hydrogencarbonate, again with water, and then with a saturated aqueous solution of sodium chloride. The aqueous washings were extracted with methylene chloride, and the organic phase was combined with the methylene chloride extract. The resulting mixture was dried over anhydrous magnesium sulphate. The solvent was removed from the mixture by distillation under reduced pressure, and the residue was purified by silica gel column chromatography, using a 14 : 1 by volume mixture of methylene chloride and methanol as the eluent, to obtain 814 mg of the title compound; as a powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1773, 1711, 1650, 1607, 1522, 1346, 854, 738.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

- 5 1.15 (3H, doubl t, J = 3.42 Hz);
- 1.18 (3H, doublet, J = 3.90 Hz);
- 2.09 (2H, doublet, J = 8.3 Hz);
- 2.17 (1H, singlet);
- 2.49 - 2.51 (1H, multiplet);
- 2.70 - 3.93 (16H, multiplet);
- 10 3.95 - 4.08 (1H, multiplet);
- 4.11 - 4.20 (1H, multiplet);
- 4.23 - 4.29 (1H, multiplet);
- 4.55 - 4.66 (1H, multiplet);
- 5.06 - 5.75 (4H, multiplet);
- 15 7.53 - 7.74 (4H, multiplet);
- 8.21 - 8.25 (4H, multiplet).

1(4 (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-((2S,4S)-2-[(3S)-3-trimethylammoniumpyrrolidin-1-yl-carbonyl]pyrrolidin-4-ylthio)-1-carbapen-2-em-3-carboxylate hydrochloride

20 771 mg of 4-nitrobenzyl (1R,5S,6S)-2-((2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio)-1-carbapen-2-em-3-carboxylate [prepared as described in step (3) above] were dissolved in 8 ml of dry acetonitrile, and 182 mg of methyl trifluoromethanesulphonate were added to the solution, whilst ice-cooling, after which the mixture was stirred
25 at the same temperature for 1 hour. The powdery product obtained by evaporating off the solvent under reduced pressure was dissolved in a mixture of 7 ml of tetrahydrofuran and 3 ml of water, after which the mixture was hydrogenated at room temperature for 1 hour in the presence of a 10% w/w palladium-on-carbon catalyst. At the end of this time, the catalyst was removed by filtration, and the tetrahydrofuran was removed by distillation under reduced pressure; the aqueous phase was then washed with diethyl ether, after which it was concentrated by evaporation under reduced pressure. The resulting residue was then subjected to ion-exchange chromatography (Dowex 1-X4, 50 to 100 mesh, C1 FORM, manufactured by Dow Chemical; "Dowex" is a trade mark), using water as the eluent. The fractions containing the desired compound were collected and freeze-dried to obtain 460 mg of a crude product as a powder.

30 The whole of this crude product was applied to a column (Cosmosil 75C₁₈-prep, manufactured by Nacalai; "Cosmosil" is a trade mark) and eluted with water. The fractions containing the desired compound were combined, concentrated by evaporation under reduced pressure, and freeze-dried to obtain 182 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1756, 1656, 1599, 1479, 1373.

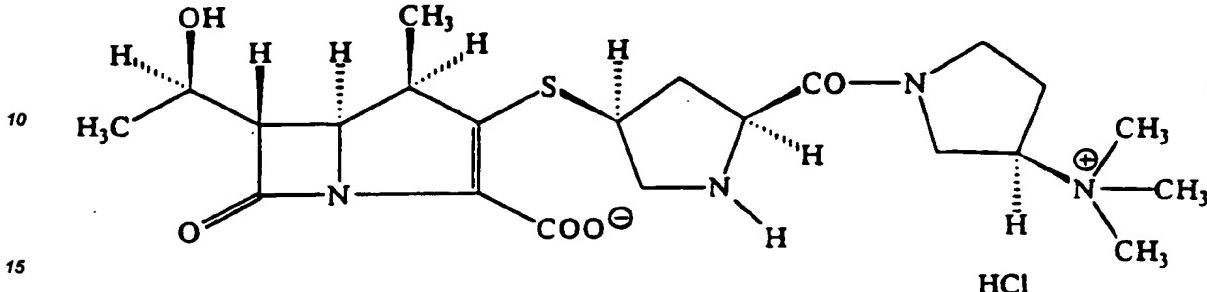
40 Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 1.21 (3H, doublet, J = 6.83 Hz);
- 1.28 (3H, doublet, J = 6.35 Hz);
- 1.95 - 2.10 (1H, multiplet);
- 45 2.40 - 2.65 (2H, multiplet);
- 3.00 - 3.15 (1H, multiplet);
- 3.21 (6H, singlet);
- 3.23 (3H, singlet);
- 3.37 (1H, doublet of doublets, J = 7.32 & 9.28 Hz);
- 50 4.20 - 4.30 (2H, multiplet);
- 3.40 - 4.20 (9H, multiplet);
- 4.65 - 4.75 (1H, multiplet).

EXAMPLE 2

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3R)-3-trimethylammoniopyrrolidin-1-ylcarbonyl]-pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

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15

2(1) (2S,4S)-2-[(3R)-3-Dimethylamino-1-pyrrolidinylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxy-carbonyl)pyrrolidine

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2.60 g of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 20 ml of dry tetrahydrofuran, and the resulting solution was cooled to -20°C. 590 mg of triethylamine and then 704 mg of pivaloyl chloride were added to the solution, after which the resulting mixture was stirred at the same temperature for 5 minutes. 2.00 g of (3R)-3-dimethylaminopyrrolidine trifluoroacetate, 788 mg of diisopropylethylamine and 20 ml of dry acetonitrile were then added, in that order, to the mixture, and the mixture was gradually heated and then stirred at 0°C for 1 hour. The reaction mixture was then filtered, and the solvent was removed by evaporation under reduced pressure. The residue was diluted with ethyl acetate, and the diluted solution was washed with an aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order. It was then dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 3 : 1 by volume mixture of acetonitrile and methanol as the eluent, to obtain 2.56 g of the title compound as a powder.

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Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1710, 1655, 1512, 1344, 1110, 857, 738.

30

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

1.28 - 3.31 (15H, multiplet);
3.40 - 3.63 (2H, multiplet);
3.72 - 3.92 (6H, multiplet);
4.36 - 4.53 (1H, multiplet);
4.95 - 5.22 (2H, multiplet);
6.88 (2H, doublet, J = 8.79 Hz);
7.27 (2H, doublet, J = 8.31 Hz);
7.51 - 7.61 (2H, multiplet);
8.18 - 8.26 (2H, multiplet).

35

2(2) (2S,4S)-2-[(3R)-3-Dimethylamino-1-pyrrolidinylcarbonyl]-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine trifluoromethanesulphonate

40

2.56 g of (2S,4S)-2-[(3R)-3-dimethylamino-1-pyrrolidinylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (1) above] were suspended in 5.1 ml of anisole, and 25.5 ml of trifluoroacetic acid and 0.83 ml of trifluoromethanesulphonic acid were added, whilst ice-cooling, to the resulting suspension. The mixture was then stirred at room temperature for 3 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, 1,2-dichloroethane was added to the residue, and the excess acid was removed by azeotropic distillation. The residue was decanted using hexane and then triturated with diethyl ether, after which the mixture was decanted and dried by evaporation under reduced pressure to give 3.65 g of the title compound as a powdery product.

2(3) 4-Nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3R)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

1.71 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 17 ml of dry acetonitrile, and 1.34 mg of diphenyl phosphorylchloride and 648 mg of diisopropylethylamine were added dropwise, whilst ice-cooling, to the resulting solution, after which the mixture was stirred at the same temperature for 1 hour. At the end of this time, a solution of 1.84 g of diisopropylethylamine and 3.65 g of (2S,4S)-2-[(3R)-3-dimethylamino-1-pyrrolidinylcarbonyl]-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine trifluoromethanesulphonate [prepared as described in step (2) above] in 35 ml of dry acetonitrile was added dropwise to the resulting mixture, after which the mixture was stirred at the same temperature for 7 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting residue was dissolved in methylene chloride. The resulting solution was washed with water, with an aqueous solution of sodium hydrogencarbonate, again with water and then with a saturated aqueous solution of sodium chloride, in that order. The aqueous washings were then extracted with methylene chloride and the organic phase was combined with the extract and dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 12 : 1 by volume mixture of methylene chloride and methanol as the eluent, to obtain 2.60 g of the title compound, as a powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

20 1773, 1712, 1652, 1608, 1523, 1346, 855, 738.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

25 1.15 (3H, doublet, J = 3.91 Hz);
 1.18 (3H, doublet, J = 4.39 Hz);
 2.07 (2H, singlet);
 2.16 (2H, doublet, J = 4.88 Hz);
 2.49 - 2.51 (1H, multiplet);
 2.7 - 4.2 (16H, multiplet);
 3.9 - 4.0 (1H, multiplet);
 4.2 - 4.3 (1H, multiplet);
 30 4.4 - 4.6 (1H, multiplet);
 5.0 - 5.5 (4H, multiplet);
 7.5 - 7.8 (4H, multiplet);
 8.2 - 8.3 (4H, multiplet).

35

2(4) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3R)-3-trimethylammoniumpyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

1.30 g of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3R)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (3) above] were dissolved in 13 ml of dry acetonitrile, and 307 mg of methyl trifluoromethanesulphonate were added to the resulting solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 1 hour. The powdery product obtained by evaporating off the solvent under reduced pressure was dissolved in a mixture of 12 ml of tetrahydrofuran and 5 ml of water, after which the mixture was hydrogenated at room temperature for 1.5 hours in the presence of 3 g of a 10% w/w palladium-on-carbon catalyst. At the end of this time, the catalyst was removed by filtration, and the tetrahydrofuran was distilled off under reduced pressure. The aqueous phase was then washed with diethyl ether and concentrated by evaporation under reduced pressure. It was then subjected to ion-exchange chromatography (Dowex 1-X4, 50 to 100 mesh, C1 FORM, manufactured by Dow Chemical), using water as the eluent. The fractions containing the desired compound were collected and freeze-dried to obtain a crude product as a powder.

This crude product was applied to a column (Cosmosil 75C₁₈-prep, manufactured by Nacalai) and eluted with water. The fractions containing the desired compound were combined, concentrated by evaporation under reduced pressure, and freeze-dried to obtain 173 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

55 1758, 1656, 1600, 1479, 1374.

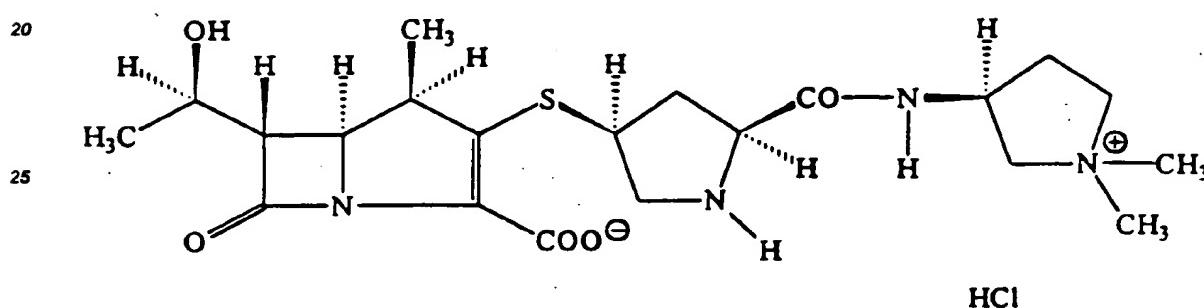
Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.21 (3H, doublet, J = 7.32 Hz);

1.28 (3H, doublet, $J = 6.35$ Hz);
 1.95 - 2.10 (1H, multiplet);
 2.45 - 2.60 (2H, multiplet);
 3.05 - 3.25 (1H, multiplet);
 5 3.20 (6H, singlet);
 3.21 (3H, singlet);
 3.37 (1H, doublet of doublets, $J = 7.32 \& 9.27$ Hz);
 3.45 - 3.55 (2H, multiplet);
 3.60 - 4.20 (9H, multiplet);
 10 4.20 - 4.35 (2H, multiplet);
 4.63 - 4.72 (1H, multiplet).

EXAMPLE 3

15 (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-1,1-Dimethyl-3-pyrrolidinioaminocarbonyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride



3(1) (2S,4S)-4-(4-Methoxybenzylthio)-2-[(3S)-1-methyl-3-pyrrolidinylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

35 7.99 g of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 80 ml of dry acetonitrile, and 3.05 g of N,N'-carbodiimidazole were added to the resulting solution, after which the mixture was stirred at room temperature for 2 hours. At the end of this time, the reaction mixture was cooled to 0°C, and then a solution of 3.34 g of (3S)-3-amino-1-t-butoxycarbonylpyrrolidine in 30 ml of dry acetonitrile was added thereto. The mixture was then stirred at the same temperature for 20 minutes, 40 at room temperature for 1.4 hours and then at 32°C for 45 minutes. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, diluted with 200 ml of ethyl acetate and then washed twice with water and twice with a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous magnesium sulphate, and the solvent was removed by distillation under reduced pressure. The residue was recrystallised from diethyl ether to obtain 9.11 g of a powder.

45 1.00 g of the powder thus obtained was mixed with 10 ml of ethyl acetate and dissolved by heating. 2.5 ml of a 4N solution of hydrogen chloride in ethyl acetate were then added to the solution, after which the mixture was heated under reflux for 30 minutes. The solvent was then removed by distillation under reduced pressure, after which ethyl acetate was added to the residue, and the solvent was again removed by distillation under reduced pressure, so as to remove the acid. The resulting residue was triturated with diethyl ether, after which the mixture was decanted. The solvent was removed by distillation under reduced pressure to obtain 630 mg of a hygroscopic powder. This procedure was repeated to obtain further quantities of the powder.

50 2.5 g of the powder thus obtained were mixed with 25 ml of dioxane, and a 2.00 ml of a 5N aqueous solution of sodium hydroxide were added to the mixture at 10°C, followed by 0.47 ml of dimethyl sulphate, after which the mixture was stirred at the same temperature for 50 minutes and then at room temperature for 40 minutes. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting residue was diluted with ethyl acetate. The resulting organic phase was washed with a saturated aqueous solution of sodium chloride. The aqueous phase was extracted with ethyl acetate, and the organic phases were combined and dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure to obtain 1.80 g of a white powder.

duced pressure, and the residue obtained was subjected to silica gel chromatography, using a gradient elution method, with mixtures of ethyl acetate and methanol ranging from 1 : 1 to 1 : 5 by volume as the eluent, to obtain 850 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

5 1713, 1648, 1523, 1346, 1244, 1030, 850, 738.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

10 1.87 - 3.71 (16H, multiplet);

3.79 (3H, singlet);

4.15 - 4.50 (2H, multiplet);

10 5.10 - 5.30 (2H, multiplet);

6.82 - 6.87 (2H, multiplet);

7.19 - 7.23 (2H, multiplet);

7.49 (2H, doublet, J = 8.79 Hz);

8.22 (2H, doublet, J = 8.30 Hz).

15

3(2) 4-Nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-1-methyl-3-pyrrolidinylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate

20 834 mg of (2S,4S)-4-(4-methoxybenzylthio)-2-[(3S)-1-methyl-3-pyrrolidinylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (1) above] were suspended in 1.7 ml of anisole, and 8.6 ml of trifluoroacetic acid and 0.28 ml of trifluoromethanesulphonic acid were added, whilst ice-cooling, to the resulting suspension, after which the mixture was stirred at room temperature for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, 1,2-dichloroethane was added to the residue, and the acid was removed by azeotropic distillation. The resulting residue was decanted with hexane and was then triturated with diethyl ether, after which the mixture was decanted and dried by evaporation under reduced pressure to give a salt as a powdery product.

25 572 mg of 4-nitrobenzyl (1R,5R,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 5.7 ml of dry acetonitrile, and 445 mg of diphenylphosphoryl chloride and 214 mg of diisopropylethylamine were added dropwise, whilst ice-cooling, to the resulting solution. The mixture was then stirred at the same temperature for 1 hour. At the end of this time, a solution of 613 mg of diisopropylethylamine and the whole of the salt obtained in the above step in 6.1 ml of dry acetonitrile was added dropwise, whilst ice-cooling, to the resulting mixture and the mixture was stirred at the same temperature for 6 hours. The solvent was then removed by distillation under reduced pressure, and the residue was dissolved in ethyl acetate. The resulting solution was then washed with water, with an aqueous solution of sodium hydrogencarbonate, again with water and finally with a saturated aqueous solution of sodium chloride. The aqueous washings were combined and extracted with ethyl acetate, and all the organic phases, including this extract, were combined and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 6 : 1 by volume mixture of methylene chloride and methanol as the eluent, to obtain 566 mg of the title compound, as a powder.

40 Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1775, 1712, 1670, 1606, 1522, 1346, 852, 737.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

45 1.15 (3H, doublet, J = 1.47 Hz);

1.17 (3H, doublet, J = 2.44 Hz);

1.39 - 3.35 (12H, multiplet);

3.29 (1H, doublet of doublets, J = 2.44 & 6.35 Hz);

3.54 - 3.66 (1H, multiplet);

3.79 - 4.32 (6H, multiplet);

5.09 - 5.48 (4H, multiplet);

50 7.57 - 7.74 (4H, multiplet);

8.19 - 8.25 (4H, multiplet).

3(3) (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-1,1-Dimethyl-3-pyrrolidinioaminocarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

55

552 mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-1-methyl-3-pyrrolidinylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in step (2) above] were dissolved in 5 ml of dry acetonitrile, and 132 mg of methyl tri-

fluorom than sulphonate were added to the solution, whilst ice-cooling. The mixture was then stirred at the same temperature for 30 minutes. The powdery product obtained by evaporation of the solvent was dissolved in a mixture of 14 ml of tetrahydrofuran and 7 ml of water, after which the mixture was hydrogenated at room temperature for 1 hour in an atmosphere of hydrogen and in the presence of 1.2 g of a 10% w/w palladium-on-carbon catalyst. At the end of this time, the catalyst was removed by filtration and the tetrahydrofuran was distilled off under reduced pressure. The aqueous phase was then washed with diethyl ether. The aqueous phase was concentrated by evaporation under reduced pressure and then subjected to ion-exchange chromatography (Dowex 1-X4, 50 to 100 mesh, C1 FORM, manufactured by Dow Chemical), using water as the eluent. The fractions containing the desired compound were collected and freeze-dried to obtain a crude product as a powder.

This crude product was applied to a column (Cosmosil 75C₁₈-prep, manufactured by Nacalai) and eluted with water. The fractions containing the desired compound were combined, concentrated and freeze-dried to obtain 187 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

15 1758, 1683, 1595, 1562, 1452, 1384.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

12 1.21 (3H, doublet, J = 7.32 Hz);

13 1.29 (3H, doublet, J = 6.35 Hz);

14 2.10 - 2.20 (1H, multiplet);

15 2.25 - 2.40 (1H, multiplet);

16 2.70 - 2.85 (1H, multiplet);

17 2.85 - 3.00 (1H, multiplet);

18 3.24 (3H, singlet);

19 3.28 (3H, singlet);

20 3.35 (1H, doublet of doublets, J = 7.33 & 9.28 Hz);

21 3.40 - 4.10 (9H, multiplet);

22 4.20 - 4.30 (2H, multiplet);

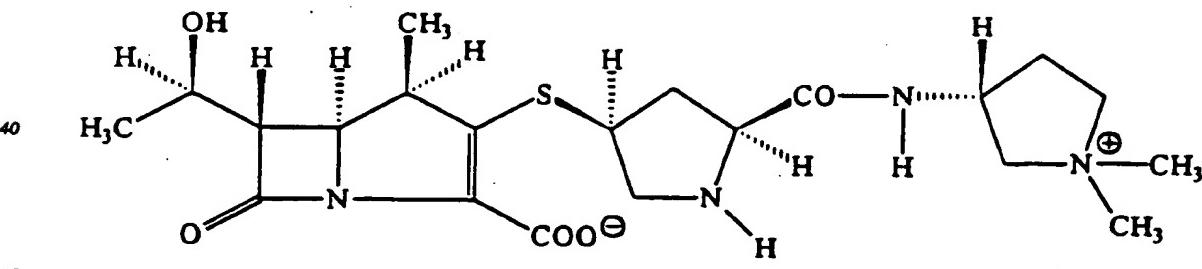
23 4.48 (1H, doublet of doublets, J = 5.86 & 9.28 Hz).

30

EXAMPLE 4

(1R,5S,6S)-2-[(2S,4S)-2-[(3R)-1,1-Dimethyl-3-pyrrolidinoaminocarbonyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

35



45

HCl

4(1)(2S,4S)-4-(4-Methoxybenzylthio)-2-[(3R)-1-methyl-3-pyrrolidinyloxymocarbonyl]-1-(4-nitrobenzyloxy-carbonyl)pyrrolidine

50

8.00 g of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxy carbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 80 ml of dry acetonitrile, and 3.05 g of N,N'-carbodiimidazole were added to the resulting solution, after which the mixture was stirred at room temperature for 2 hours. At the end of this time, the reaction mixture was cooled to 0°C, and then a solution of 3.67 g of (3R)-3-amino-1-t-butoxycarbonylpiperidine in 7 ml of dry acetonitrile was added to the mixture, which was then stirred at the same temperature for 10 minutes and then at room temperature for 2 hours. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure. The resulting residue was diluted with 200 ml of ethyl acetate and then washed twice, each time with 100 ml of water, and once with 100 ml of a saturated aqueous solution of sodium

chlorid . The organic phase was dried over anhydrous magnesium sulphate, the solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography, using a 3 : 1 by volume mixture of ethyl acetate and cyclohexane as the eluent, to obtain 9.26 g of a white powder.

4.80 g of this powder were dissolved in 45 ml of ethyl acetate, and 15.6 ml of a 4N solution of hydrogen chloride in ethyl acetate were added to the resulting solution. The mixture was then heated under reflux for 30 minutes, after which the solvent was removed by distillation under reduced pressure. Ethyl acetate was added to the residue, and then the solvent was distilled off, so as to remove the acid. The residue thus obtained was triturated with diethyl ether, after which the mixture was decanted. The solvent was then removed by distillation under reduced pressure to obtain 4.47 g of a white powder.

10 1.98 g of this powder were mixed with 20 ml of dioxane, and 1.58 ml of a 5N aqueous solution of sodium hydroxide and 0.41 ml of dimethyl sulphate were added at 10°C to the mixture, after which the mixture was stirred at the same temperature for 30 minutes. At the end of this time, the solvent was removed by distillation under reduced pressure, the residue was diluted with ethyl acetate, and the resulting organic phase was washed with a saturated aqueous solution of sodium chloride. The aqueous washings were extracted with ethyl acetate. The organic phase was combined with the resulting extract, and the mixture was dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, and the resulting residue was subjected to silica gel chromatography, using a 1 : 5 by volume mixture of ethyl acetate and methanol as the eluent, to obtain 550 mg of the title compound as a powder.

20 4(2) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3R)-1-methyl-3-pyrrolidinylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio)-1-carbapen-2-em-3-carboxylate

550 mg of (2S,4S)-4-(4-methoxybenzylthio)-2-[(3R)-1-methyl-3-pyrrolidinylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (1) above] were suspended in 1.1 ml of anisole, and 5.5 ml of trifluoroacetic acid and 0.18 ml of trifluoromethanesulphonic acid were added to the resulting suspension, whilst ice-cooling, after which the mixture was stirred at room temperature for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, 1,2-dichloroethane was added to the residue, and the acid was removed by azeotropic distillation. The residue was decanted with hexane and then triturated with diethyl ether, after which the mixture was decanted and dried by evaporation under reduced pressure, to give a salt as a powdery product.

377 mg of 4-nitrobenzyl (1R,5R,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate was dissolved in 3.7 ml of dry acetonitrile, and 293 mg of diphenylphosphoryl chloride and 141 mg of diisopropylethylamine were added dropwise to the resulting solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 1 hour. At the end of this time, a solution of 403 mg of diisopropylethylamine and the whole of the salt obtained in the above step in 4 ml of dry acetonitrile was added dropwise to the resulting mixture, whilst ice-cooling. The resulting mixture was stirred at the same temperature for 1 hour and then left to stand in a refrigerator overnight. At the end of this time, the mixture was stirred at room temperature for 1.5 hours and the solvent was removed by distillation under reduced pressure. The resulting residue was dissolved in 10 ml of methylene chloride, after which the mixture was washed with water, with an aqueous solution of sodium hydrogen carbonate, again with water and finally with a saturated aqueous solution of sodium chloride, in that order. The aqueous washings were dried over anhydrous magnesium sulphate and the solvent was removed by distillation under reduced pressure. The resulting residue was purified by silica gel column chromatography, using a 3 : 1 : 3 by volume mixture of ethyl acetate, methylene chloride and methanol as the eluent, to obtain 230 mg of the title compound as a powder.

45 Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1775, 1712, 1670, 1617, 1522, 1345, 853, 738.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

50 1.15 (3H, doublet, J = 1.15 Hz);
1.17 (3H, doublet, J = 1.95 Hz);
1.47 - 1.56 (1H, multiplet);
1.72 - 1.75 (1H, multiplet);
1.98 - 3.39 (17H, multiplet);
3.54 - 3.62 (1H, multiplet);
3.84 - 4.34 (6H, multiplet);
5.08 - 5.49 (4H, multiplet);
7.57 - 7.74 (4H, multiplet);
8.19 - 8.25 (4H, multiplet).

4(3) (1R,5S,6S)-2-[(2S,4S)-2-[(3R)-1,1-Dimethyl-3-pyrrolidinoaminocarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

230 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3R)-1-methyl-3-pyrrolidinyloaminocarbonyl]-1-(4-nitrobenzoyloxycarbonyl)pyrrolidin-4-ylthio)-1-carbapen-2-em-3-carboxylate [prepared as described in step (2) above] were dissolved in 2 ml of dry acetonitrile, and 55.3 mg of methyl trifluoromethanesulphonate were added to the solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 30 minutes. The powdery product obtained by evaporation of the solvent was dissolved in a mixture of 7 ml of tetrahydrofuran and 3 ml of water, after which the mixture was hydrogenated at room temperature for 0.5 hour in an atmosphere of hydrogen and in the presence of 0.6 g of a 10% w/w palladium-on-carbon catalyst. At the end of this time, the catalyst was removed by filtration and the tetrahydrofuran was removed by distillation under reduced pressure. The aqueous residue was then washed with diethyl ether, concentrated by evaporation under reduced pressure and then subjected to ion-exchange chromatography (Dow x 1-X4, 50 to 100 mesh, C1 FORM, manufactured by Dow Chemical), using water as the eluent. Those fractions containing the desired compound were collected and freeze-dried to give a crude product as a powder.

This crude product was applied to a column (Cosmosil 75C₁₈-prep, manufactured by Nacalai) and eluted with water. Those fractions containing the desired compound were combined, concentrated by evaporation under reduced pressure, and freeze-dried to obtain 42 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

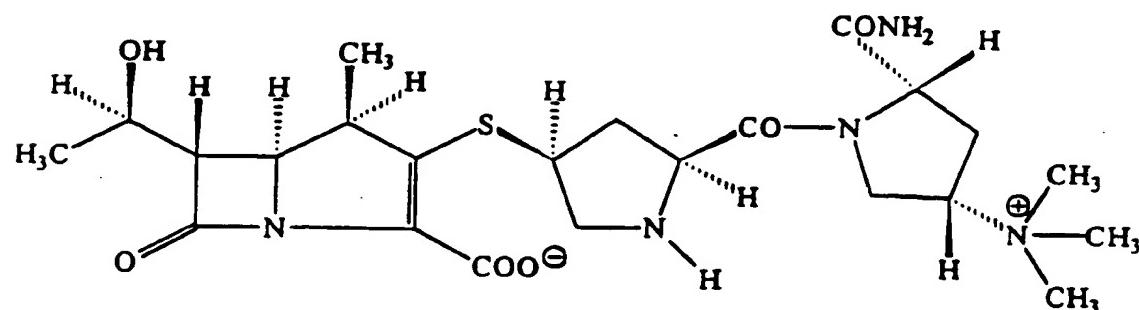
1758, 1683, 1593, 1559, 1458, 1386.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.20 (3H, doublet, J = 6.83 Hz);
 1.28 (3H, doublet, J = 6.35 Hz);
 2.11 - 2.35 (2H, multiplet);
 2.71 - 3.02 (2H, multiplet);
 3.20 (3H, singlet);
 3.27 (3H, singlet);
 3.34 (1H, doublet of doublets, J = 7.33 & 9.28 Hz);
 3.45 - 4.09 (9H, multiplet);
 4.21 - 4.27 (2H, multiplet);
 4.51 (1H, doublet of doublets, J = 6.84 & 9.28 Hz).

EXAMPLE 5

(1R,5S,6S)-2-[(2S,4S)-2-[(2S,4S)-2-Carbamoyl-4-trimethylammoniumpyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate



866 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 8 ml of dry acetonitrile, and 520 μ l of diphenylphosphoryl chloride and 437 μ l of diisopropylethylamin were added dropwise to the resulting solution, whilst ice-cooling. The mixture was then stirred at the same temperature for 45 minutes. At the end of this time, a solution of 895 μ l of diisopropylethylamine and 1.62 g of (2S,4S)-2-[(2S,4S)-2-carbamoyl-4-dimethylaminopyrrolidin-1-ylcarbonyl]-4-mercaptop-1-(4-nitrobenzoyloxycarbonyl)pyrrolidin trifluoromethanesulphonate in 7 ml of dry acetonitrile was added dropwise, whilst ice-cooling, to the mixture. The resulting mixture was then stirred at the same temperature for 30 min-

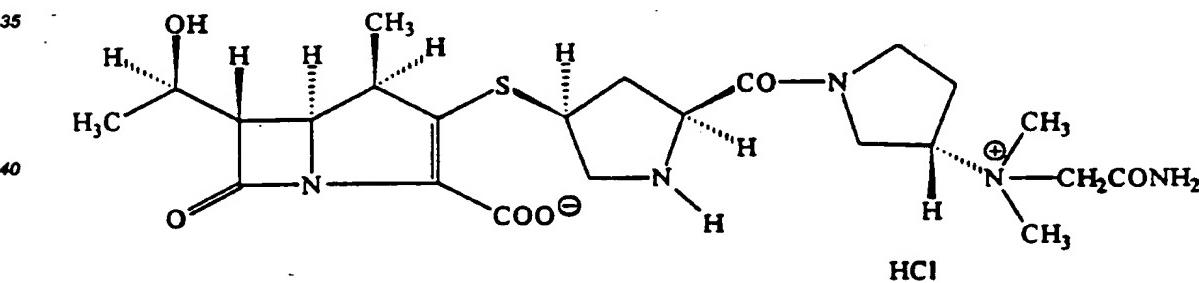
utes, after which it was left to stand overnight, whilst ice-cooling. The mixture was then treated in the same manner as described in Example 1(2), and was subjected to silica gel column chromatography. The fractions obtained by a gradient elution method, using mixtures of ethyl acetate and methanol ranging from 80 : 20 to 70 : 30 by volume as the eluent, were combined and concentrated by evaporation under reduced pressure, to obtain 521 mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(2S,4S)-2-carbamoyl-4-dimethylaminopyrrolidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate as a pale brown powder. 505 mg of this compound were dissolved in 6 ml of dry acetonitrile, and 81 μ l of methyl fluorosulphonate were added dropwise, whilst ice-cooling, to the resulting solution, after which the mixture was stirred at the same temperature for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting crude product was hydrogenated, treated and purified in the same manner as described in Example 1(4), to obtain 161 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:
 1754, 1668, 1600, 1436, 1382, 1288, 1264, 1225.
 Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:
 298.0.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:
 1.04 (3H, doublet, J = 6.84 Hz);
 1.15 (3H, doublet, J = 6.35 Hz);
 2.05 - 2.17 (1H, multiplet);
 2.47 - 2.65 (3H, multiplet);
 2.96 - 3.19 (2H, multiplet);
 3.07 (9H, singlet);
 3.52 - 3.78 (4H, multiplet);
 3.84 - 4.07 (3H, multiplet);
 4.21 - 4.34 (1H, multiplet);
 4.40 - 4.56 (2H, multiplet).

EXAMPLE 6

(1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-(Carbamoylmethyldimethylammonio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride



1.00 g of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in Example 1(3)] was dissolved in 10 ml of dry acetonitrile, and 1.21 g of 2-iodoacetamide were added to the resulting solution, after which the mixture was stirred at 70°C for 1.5 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was washed by decantation with diethyl ether and dried by evaporation under reduced pressure to obtain 1.28 g of a powder. The whole of this compound was dissolved in a mixture of 12 ml of tetrahydrofuran and 12 ml of water, and 1.00 g of a 10% w/w palladium-on-carbon catalyst was added to the solution. The mixture was then hydrogenated at room temperature for 2 hours. At the end of this time, the reaction mixture was treated, purified and freeze-dried in the same manner as described in Example 1(4), to obtain 155 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:
 1758, 1695, 1656, 1600, 1469, 1375, 1286, 1226, 1182.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

296.9

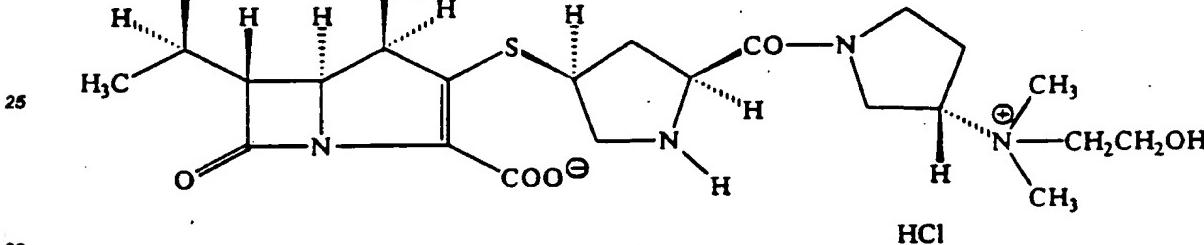
Nuclear Magnetic Resonance Spectrum (hexad D_2O tetradeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

- 5 1.14 (3H, doublet, $J = 6.84$ Hz);
- 1.15 (3H, doublet, $J = 6.34$ Hz);
- 1.52 - 1.74 (1H, multiplet);
- 2.18 - 2.94 (4H, multiplet);
- 3.19 (1H, doublet of doublets, $J = 6.35$ & 2.44 Hz);
- 3.25 (3H, singlet);
- 10 3.26 (3H, singlet);
- 3.25 - 4.25 (15H, multiplet);
- 4.44 - 4.63 (1H, multiplet);
- 5.08 (1H, broad singlet).

15 **EXAMPLE 7**

(1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-[(2-Hydroxyethyl)dimethylammonio]pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylothio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

20



30

35 1.68 g of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzoyloxycarbonyl)pyrrolidin-4-ylothio)-1-carbapen-2-em-3-carboxylate [prepared as described in Example 1(3)] were dissolved in 12 ml of dry acetonitrile, and 1.68 g of 2-iodoethanol were added to the resulting solution, after which the mixture was stirred at 70°C to 75°C for 6.5 hours. The solvent was then removed by distillation under reduced pressure, and the residue was washed by decantation with diethyl ether and dried by evaporation under reduced pressure to obtain 1.66 g of a powdery product. The whole of this compound was dissolved in a mixture of 15 ml of tetrahydrofuran and 15 ml of water, and 1.20 g of a 10% w/w palladium-on-carbon catalyst were added to the solution, after which the mixture was hydrogenated at room temperature for 2 hours. At the end of this time, the reaction mixture was treated, purified and freeze-dried in the same manner as described in Example 1(4), to obtain 250 mg of the title compound as a colourless powder.

40 Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:
1758, 1658, 1599, 1469, 1374, 1286, 1258, 1227, 1148.

45 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:
296.2.

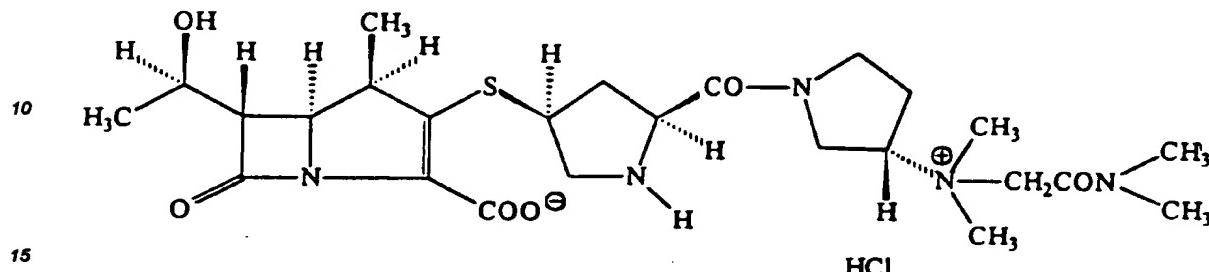
Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 50 1.21 (3H, doublet, $J = 6.84$ Hz);
- 1.29 (3H, doublet, $J = 6.34$ Hz);
- 1.96 - 2.13 (1H, multiplet);
- 2.30 - 2.64 (2H, multiplet);
- 2.94 - 3.16 (1H, multiplet);
- 3.22 & 3.25 (together 6H, two singlets);
- 3.25 - 3.70 (6H, multiplet);
- 3.72 - 4.84 (11H, multiplet).

EXAMPLE 8

(1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-[N-(N,N-Dimethylcarbamoylmethyl)-N,N-dimethylammoni pyrrolidin-1-yl carbonyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

5



500 mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-dimethylamino-1-pyrrolidinylcarbonyl]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio)-1-carbapen-2-em-3-carboxylate [prepared as described in Example 1(3)] were dissolved in 5 ml of dry acetonitrile, and 700 mg of 2-iodo-N,N-dimethylacetamide were added to the resulting solution, after which the mixture was stirred at 80°C for 4 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was washed with diethyl ether and dried by evaporation under reduced pressure to obtain 670 mg of a powdery product. The whole of this compound was dissolved in a mixture of 10 ml of tetrahydrofuran and 8 ml of water, and 2.0 g of a 10% w/w palladium-on-carbon catalyst were added to the resulting solution. The mixture was then hydrogenated at 28 to 30°C for 2 hours. At the end of this time, the reaction mixture was treated, purified and freeze-dried in the same manner as described in Example 1(4), to obtain 82 mg of the title compound as a colourless powder.

30 Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1759, 1657, 1603, 1461, 1370, 1147.

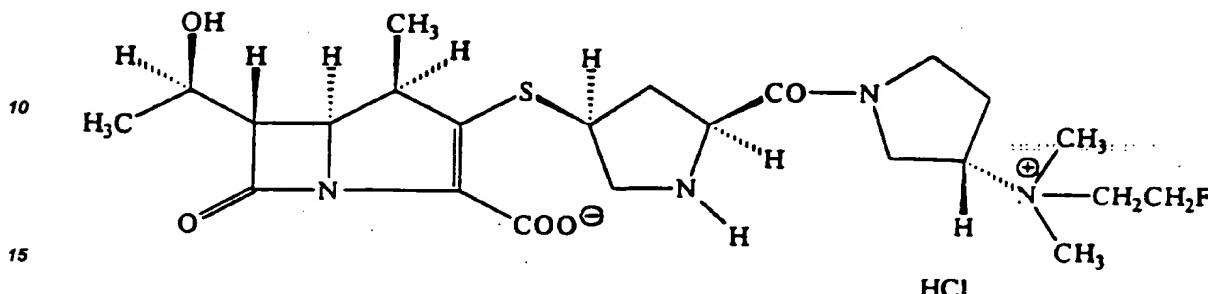
Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 35 1.21 (3H, doublet, J = 6.8 Hz);
- 1.28 (3H, doublet, J = 6.4 Hz);
- 1.98 - 2.07 (1H, multiplet);
- 2.49 - 2.56 (2H, multiplet);
- 2.97 (3H, singlet);
- 3.03 (3H, singlet);
- 40 2.95 - 3.13 (1H, multiplet);
- 3.37 (6H, singlet);
- 3.31 - 3.51 (3H, multiplet);
- 3.54 - 3.66 (1H, multiplet);
- 3.75 - 3.89 (2H, multiplet);
- 45 3.92 - 3.97 (2H, multiplet);
- 4.02 - 4.17 (1H, multiplet);
- 4.20 - 4.29 (2H, multiplet);
- 4.47 (2H, singlet);
- 4.69 - 4.81 (1H, multiplet);
- 50 4.86 - 4.98 (1H, multiplet).

EXAMPLE 9

(1R,5S,6S)-2-[(2S,4S)-2-((3S)-3-[N-(2-Fluoroethyl)-N,N-dimethylamino]methyl)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

5



501 mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-((3S)-3-dimethylamino-1-pyrrolidinylcarbonyl)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in Example 1(3)] were dissolved in 3 ml of dry acetonitrile, and 495 mg of sodium iodide and 419 mg of 1-bromo-2-fluoroethane were added to the resulting solution, after which the mixture was heated under reflux for 13 hours. At the end of this time, the reaction mixture was filtered, and the solvent was removed from the filtrate by distillation under reduced pressure, to obtain 631 mg of a powdery product. The whole of this compound was dissolved in a mixture of 10 ml of tetrahydrofuran and 6 ml of water, and the resulting solution was subjected to hydrogenation at room temperature for 1.5 hours in the presence of 1.2 g of a 10% w/w palladium-on-carbon catalyst. The reaction mixture was then treated, purified and freeze-dried in the same manner as described in Example 1(4), to obtain 36.0 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr) ν_{\max} cm⁻¹:

30 1758, 1656, 1599, 1470, 1375.

Ultraviolet Absorption Spectrum (H₂O), λ_{\max} nm:

296.8.

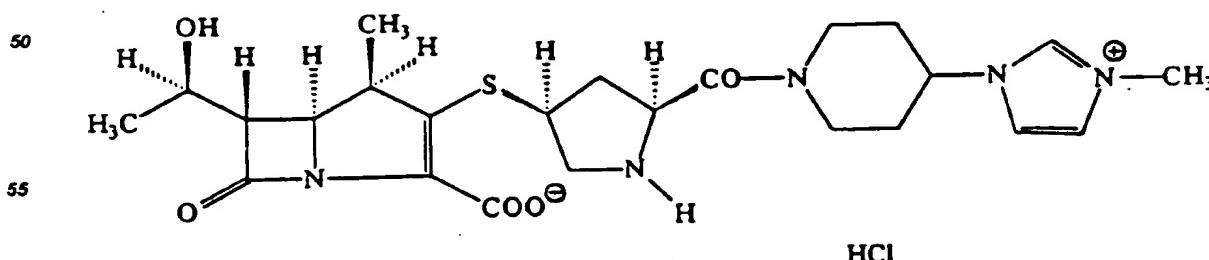
Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

35 1.22 (3H, doublet, J = 7.26 Hz);
1.30 (3H, doublet, J = 6.59 Hz);
1.97 - 2.10 (1H, multiplet);
2.40 - 2.65 (2H, multiplet);
3.00 - 3.15 (1H, multiplet);
40 3.26 (4H, singlet);
3.28 (2H, singlet);
3.30 - 5.20 (17H, multiplet).

EXAMPLE 10

45

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[4-(3-methylimidazolio)piperidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride



10(1) (2S,4S)-2-[4-(imidazol-1-yl)piperidin-1-ylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

1520 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid
 5 were dissolved in 15 ml of dry acetonitrile, and 660 mg of N,N'-carbonyldiimidazole were added to the resulting solution, after which the mixture was stirred at room temperature for 30 minutes. At the end of this time, a solution of 538 mg of 4-(imidazol-1-yl)piperidine in 5 ml of dry acetonitrile was added to the resulting mixture, and the solution was stirred at room temperature for 30 minutes and then at 40°C for 7 hours. The reaction mixture was then concentrated by evaporation under reduced pressure. The resulting residue was dissolved in ethyl acetate, washed with an aqueous solution of sodium hydrogencarbonate, with water and with an aqueous solution of sodium chloride, in that order, after which the mixture was dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was subjected to column chromatography using a reverse phase silica gel column (Cosmosil 75C₁₈-PREP, 200 ml, manufactured by Nacalai Kagaku), eluted with mixtures of acetonitrile and water ranging from 50 : 50 to 55 : 45 by volume.
 10 The fractions containing the title compound were collected and concentrated by evaporation under reduced pressure, to obtain 1450 mg of the title compound as a powder.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1709, 1655, 1609, 1512, 1345, 1246, 1110.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

20 1.70 - 1.95 (2H, multiplet);
 2.05 - 2.23 (3H, multiplet);
 2.40 - 2.55 (1H, multiplet);
 2.60 - 2.85 (1H, multiplet);
 3.03 - 3.43 (3H, multiplet);
 25 3.73 (3H, singlet);
 3.77 - 4.25 (5H, multiplet);
 4.59 - 4.84 (2H, multiplet);
 5.02 - 5.35 (2H, multiplet);
 6.85 (2H, doublet, J = 8.8 Hz);
 30 6.96 (1H, singlet);
 7.07 & 7.09 (together 1H, two singlets);
 7.23 (2H, doublet, J = 8.8 Hz);
 7.47 (2H, doublet, J = 8.8 Hz);
 7.56 (1H, singlet);
 35 8.23 (2H, doublet, J = 8.8 Hz).

10(2) (2S,4S)-2-[4-(imidazol-1-yl)piperidin-1-ylcarbonyl]-4-mercaptopyrrolidine

1.44 g of (2S,4S)-2-[4-(imidazol-1-yl)piperidin-1-ylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (1) above] were dissolved in a mixture of 1.5 ml of anisole and 7.5 ml of trifluoroacetic acid, and 350 μl of trifluoromethanesulphonic acid were added to the resulting solution, whilst ice-cooling. The resulting mixture was then stirred at room temperature for 1 hour and then at 35°C for 30 minutes, after which it was concentrated by evaporation under reduced pressure. The resulting residue was washed with diethyl ether four times to give a colourless powder. The whole of this powder was suspended in ethyl acetate, and the suspension was made alkaline by the addition of an aqueous solution of sodium hydrogencarbonate. The ethyl acetate phase was separated and washed with an aqueous solution of sodium chloride, after which this phase was dehydrated over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, to give 1150 mg of the title compound, as a colourless powder.

50 Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

1.55 - 1.85 (3H, multiplet);
 2.00 - 2.11 (2H, multiplet);
 2.63 - 2.89 (2H, multiplet);
 3.05 - 3.30 (4H, multiplet);
 3.92 - 4.15 (2H, multiplet);
 4.25 - 4.59 (2H, multiplet);
 4.71 - 4.92 (1H, multiplet);
 5.03 - 5.27 (2H, multiplet);

6.92 - 8.28 (7H, multiplet).

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1705, 1652, 1523, 1442, 1347, 1268, 1170, 1035.

5 10(3) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[4-(imidazol-1-yl)piperidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate

910 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 10 ml of dry acetonitrile, and 560 μ l of diphenylphosphoryl chloride and 470 μ l of diisopropylethylamine were added dropwise, whilst ice-cooling, to the resulting solution, after which the mixture was stirred at the same temperature for 30 minutes. A solution of 1140 mg of (2S,4S)-2-[4-(imidazol-1-yl)piperidin-1-ylcarbonyl]-4-mercaptopyrrolidine [prepared as described in step (2) above] in 10 ml of acetonitrile and 435 μ l of diisopropylethylamine were then added dropwise to the resulting mixture. The mixture was then stirred, whilst ice-cooling for 2 hours, after which it was left to stand at 4°C overnight. At the end of this time, the reaction mixture was diluted with an equivalent amount of water, and then 800 mg of sodium hydrogen-carbonate were added thereto. The mixture was then subjected to column chromatography using a reverse phase silica gel column (Cosmosil 75C₁₈-PREP, 200 ml, manufactured by Nacalai), eluted with a 1 : 1 by volume mixture of acetonitrile and water. The desired fractions were collected and concentrated by evaporation under reduced pressure, to obtain 1.40 g of the title compound as a powder.

20 Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

1.12 - 1.20 (6H, multiplet);

1.58 - 1.90 (3H, multiplet);

1.91 - 2.06 (2H, multiplet);

2.62 - 2.79 (1H, multiplet);

2.80 - 2.97 (1H, multiplet);

3.06 - 3.37 (4H, multiplet);

3.55 - 3.70 (1H, multiplet);

3.71 - 3.93 (1H, multiplet);

3.94 - 4.56 (5H, multiplet);

4.74 - 4.97 (1H, multiplet);

5.04 - 5.49 (5H, multiplet);

6.81 - 8.28 (11H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1773, 1710, 1656, 1522, 1346, 1208.

35 10(4) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[4-(3-methylimidazolio)piperidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

1000 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[4-(imidazol-1-yl)piperidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in step (3) above] were dissolved in 10 ml of dry acetonitrile, and 150 μ l of methyl trifluoromethanesulphonate were added dropwise, whilst ice-cooling, to the resulting solution, after which the mixture was stirred at the same temperature for 10 minutes and then at room temperature for 30 minutes. The reaction mixture was then concentrated by distillation under reduced pressure, and the resulting residue (1213 mg) was dissolved in a mixture of 20 ml of tetrahydrofuran and 15 ml of water. 1.3 g of a 10% w/w palladium-on-carbon catalyst were added to the resulting solution, after which the mixture was vigorously stirred at 28°C to 30°C for 1.7 hours in an atmosphere of hydrogen gas. At the end of this time, the catalyst was removed by filtration, and the filtrate was washed with diethyl ether (three times, each time with 100 ml). The aqueous phase was concentrated by evaporation under reduced pressure and then subjected to ion-exchange column chromatography (Dowex 1-X4, Model-C1, 30 ml), eluted with water. The fraction containing the title compound was concentrated by evaporation under reduced pressure, and subjected to column chromatography using a reverse phase silica gel column (Cosmosil 75C₁₈-PREP, 50 ml), eluted with water. The active fractions were collected and freeze-dried, to obtain 260 mg of the title compound as a colourless powder.

Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

55 297.

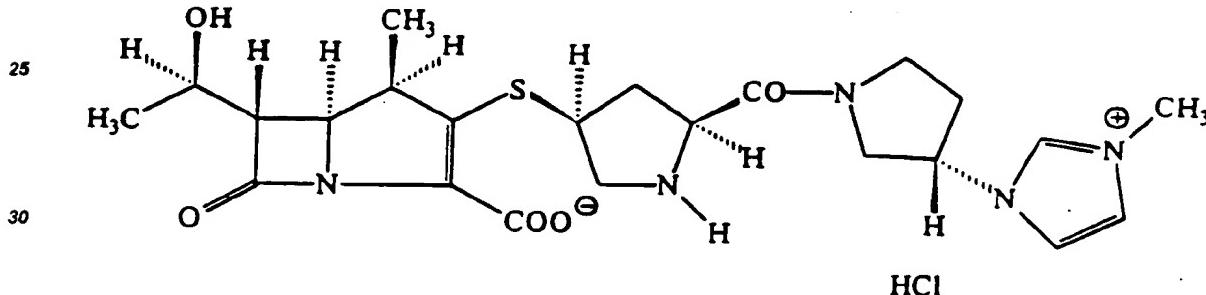
Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.22 (3H, doublet, $J = 7.3$ Hz);

- 1.29 (3H, d, *ublet*, *J* = 6.0 Hz);
 1.88 - 2.09 (3H, multiplet);
 2.28 - 2.43 (2H, multiplet);
 2.96 - 3.16 (2H, multiplet);
 5 3.33 - 3.55 (4H, multiplet);
 3.73 - 3.84 (1H, multiplet);
 3.90 (3H, singlet);
 3.91 - 4.12 (2H, multiplet);
 4.20 - 4.31 (2H, multiplet);
 10 4.55 - 4.73 (2H, multiplet);
 4.83 - 4.93 (1H, multiplet);
 7.47 (1H, singlet);
 7.57 - 7.60 (1H, multiplet);
 8.85 (1H, doublet, *J* = 7.9 Hz).
- 15 Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:
 1758, 1652, 1599, 1374, 1271, 1233, 1166.

EXAMPLE 11

- 20 (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3S)-3-(3-methylimidazolio)pyrrolidin-1-ylcarbo-nyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride



- 35 11(1) (2S,4S)-2-[(3R)-3-(Imidazol-1-yl)pyrrolidin-1-ylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxy-carbonyl)pyrrolidine

A procedure similar to that described in Example 10(1) was repeated, except that 2500 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid and 805 mg of (3R)-3-(imidazolyl-1-yl)pyrrolidine were used, to obtain 2540 mg of the title compound.

40 Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹:

1708, 1656, 1609, 1512, 1438, 1404, 1345, 1246, 1173, 1110.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 45 1.88 - 2.05 (1H, multiplet);
 2.15 - 2.31 (1H, multiplet);
 2.36 - 2.57 (2H, multiplet);
 3.02 - 3.18 (1H, multiplet);
 3.31 - 3.40 (1H, multiplet);
 3.49 - 3.63 (1H, multiplet);
 50 3.73 & 3.74 (together 2H, two singlets);
 3.78 & 3.79 (together 3H, two singlets);
 3.80 - 4.08 (3H, multiplet);
 4.26 - 4.48 (2H, multiplet);
 4.71 - 4.89 (1H, multiplet);
 55 5.00 - 5.34 (2H, multiplet);
 6.76 - 7.60 (9H, multiplet);
 8.15 - 8.27 (2H, multiplet).

11(2) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(3R)-3-(imidazolyl-1-yl)pyrrolidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate

5 2.5 g of (2S,4S)-2-[(3R)-3-(imidazolyl-1-yl)pyrrolidin-1-ylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (1) above] were reacted and treated in the same manner as described in Example 10(2) and 10(3), to obtain 2.31 g of the title compound, as a powder.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 10 1.25 - 1.39 (6H, multiplet);
- 15 2.00 - 2.80 (4H, multiplet);
- 20 3.25 - 4.96 (13H, multiplet);
- 25 5.05 - 5.53 (4H, multiplet);
- 30 6.82 - 8.29 (11H, multiplet).

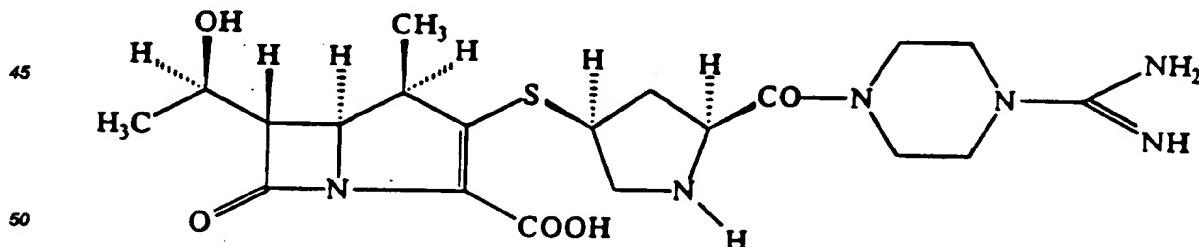
11(3) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3S)-3-(3-methylimidazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

12 1.2 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[(3R)-3-(imidazolyl-1-yl)pyrrolidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in step (2) above] were reacted and treated in the same manner as described in Example 10(4), to obtain 340 mg of the title compound as a colourless powder.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 17 1.19 - 1.31 (6H, multiplet);
- 22 1.82 - 2.07 (1H, multiplet);
- 27 2.40 - 2.58 (1H, multiplet);
- 32 2.60 - 2.80 (1H, multiplet);
- 37 2.92 (1H, multiplet);
- 42 3.32 - 3.51 (3H, multiplet);
- 47 3.71 - 4.31 (11H, multiplet);
- 52 3.60 - 3.75 (1H, multiplet);
- 57 5.17 - 5.27 (1H, multiplet);
- 62 7.50 & 7.54 (together 1H, two singlets);
- 67 7.60 (1H, singlet);
- 72 8.90 & 8.92 (together 1H, two singlets).

35 Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:
297.

EXAMPLE 1240 (1R,5S,6S)-2-[(2S,4S)-2-(4-Aminopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid55 12(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

290 μl of diphenylphosphoric acid chloride and 244 μl of diisopropylethylamine were added dropwise, whilst ice-cooling, to a solution of 471 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-

1-carbapenam-3-carboxylate in 5 ml of dry acetonitrile, and the resulting mixture was stirred at the same temperature for 1 hour. At the end of this time, a solution of 910 mg of (2S,4S)-4-mercapto-2-[4-(4-nitrobenzyl oxy carbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyl oxy carbonyl)pyrrolidine trifluoromethanesulphonate (prepared as described in Preparation 1) in 7 ml of dry acetonitrile and 500 µl of diisopropylethylamine were added dropwise, whilst ice-cooling, to the mixture, and the resulting mixture was left to stand overnight at the same temperature. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the resulting residue was diluted with ethyl acetate, after which the mixture was washed with an aqueous solution of sodium hydrogencarbonate, with water and with an aqueous solution of sodium chloride. The ethyl acetate layer was dehydrated over anhydrous sodium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography [silica gel 60 (Art. 9385), manufactured by Merck, 150 ml], eluted with mixtures of ethyl acetate and acetonitrile in proportions of 8 : 2, 7 : 3 and 6 : 4, in that order. The fractions containing the desired compound were collected and concentrated by evaporation under reduced pressure, to obtain 691 mg of the title compound, as an amorphous powder.

15 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1773, 1710, 1652, 1607, 1552, 1441, 1347.

20 Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

1.12 - 1.21 (6H, multiplet);
 1.62 - 1.78 (1H, multiplet);
 2.77 - 2.93 (1H, multiplet);
 3.11 - 4.30 (15H, multiplet);
 4.79 & 4.88 (together 1H, two triplets, J = 7.8 Hz);
 5.07 - 5.49 (6H, multiplet);
 7.52 - 7.73 (6H, multiplet);
 8.19 - 8.25 (6H, multiplet).

12(2) (1R,5S,6S)-2-[(2S,4S)-2-(4-Amidinopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

30 680 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[4-(4-nitrobenzyl oxy carbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyl oxy carbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] were dissolved in 40 ml of a 1 : 1 by volume mixture of tetrahydrofuran and water, and 950 mg of a 10% w/w palladium-on-carbon catalyst were added to the resulting solution. The mixture was then hydrogenated in an atmosphere of hydrogen at 28°C for 1 hour. At the end of this time, the catalyst was removed by filtration, and the filtrate was washed with diethyl ether. The aqueous layer was then concentrated by evaporation under reduced pressure, to 10 ml. The resulting solution was subjected to reverse phase silica gel column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque, 30 ml), eluted with mixtures of acetonitrile and water in proportions of 0 : 100, 2 : 98, 4 : 96 and 6 : 94, in that order. The fractions containing the desired compound were collected, concentrated by evaporation under reduced pressure, and freeze-dried to obtain 211 mg of the title compound as a powder.

40 Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

299.

45 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1754, 1649, 1605, 1450, 1389, 1251.

50 Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.22 (3H, doublet, J = 7.3 Hz);
 1.30 (3H, doublet, J = 6.4 Hz);
 1.64 (1H, doubled doublet of doublets, J = 13.7, 6.8 & 5.4 Hz);
 2.74 (1H, doublet of triplets, J = 13.7 & 8.8 Hz);
 3.07 (1H, doublet of doublets, J = 12.2 & 3.4 Hz);
 3.17 (1H, doublet of doublets, J = 12.2 & 5.4 Hz);
 3.34 - 3.47 (2H, multiplet);
 3.54 - 3.90 (9H, multiplet);
 4.13 (1H, doublet of doublets, J = 8.8 & 6.8 Hz);
 4.19 - 4.13 (2H, multiplet).

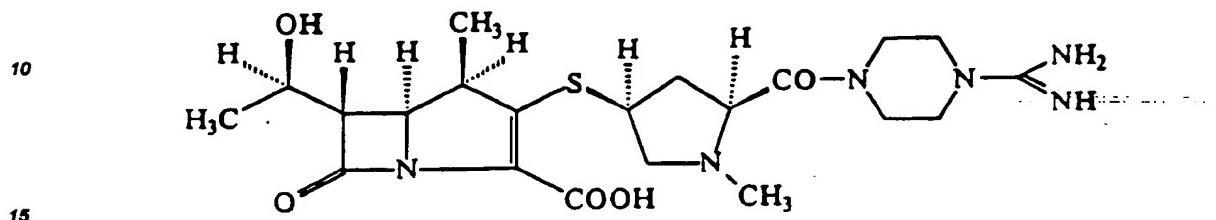
55 Nuclear Magnetic Resonance Spectrum (¹³C, D₂O, external standard: tetramethylsilane) δ ppm:

16.0, 20.2, 35.5, 41.3, 42.6, 42.8, 43.5, 44.2, 44.7, 53.9, 56.0, 57.4, 58.4, 65.2, 132.0, 140.9, 156.6,

167.8, 172.5, 176.4.

EXAMPLE 13

- 5 (1R,5S,6S)-2-[(2S,4S)-2-(4-Amidinopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



- 13(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

20 1600 mg of 4-nitrobenzyl (1R,5S,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) were dissolved in 16 ml of dry acetonitrile, and a solution of 1120 mg of (2S,4S)-4-mercaptop-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 2) in 11 ml of dry acetonitrile and 430 µl of diisopropylethylamine were added dropwise to the resulting solution, whilst ice-cooling. The resulting mixture was stirred at the same temperature overnight, after which it was concentrated by evaporation under reduced pressure. The resulting residue was diluted with ethyl acetate, and the mixture was washed with an aqueous solution of sodium hydrogencarbonate, with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was dehydrated over anhydrous sodium sulphate and then concentrated by evaporation under reduced pressure. The resulting residue was subjected to reverse phase silica gel column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque, 300 ml), eluted with a 1 : 1 by volume mixture of acetonitrile and water. The fractions containing the desired compound were collected and concentrated by evaporation under reduced pressure, to obtain 1520 mg of the title compound, as a powder.

25 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

30 1771, 1708, 1648, 1606, 1544, 1521, 1448, 1347.

35 Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide, 270 MHz) δ ppm:

1.10 - 1.20 (6H, multiplet);
 1.58 - 1.69 (1H, multiplet);
 2.24 (3H, singlet);
 2.60 - 2.80 (2H, multiplet);
 2.95 - 3.02 (1H, multiplet);
 3.20 - 3.88 (12H, multiplet);
 3.90 - 4.05 (1H, multiplet);
 4.21 (1H, doublet of doublets, J = 9.3 & 2.4 Hz);
 5.05 (1H, doublet, J = 5.4 Hz);
 5.13 (2H, singlet);
 5.29 (2H, doublet, J = 13.7 Hz);
 5.45 (2H, doublet, J = 13.7 Hz);
 7.59 (2H, doublet, J = 8.8 Hz);
 7.73 (2H, doublet, J = 8.8 Hz);
 7.90-8.20 (2H, broad);
 8.21 (2H, doublet, J = 8.8 Hz);
 8.23 (2H, doublet, J = 8.8 Hz).

- 55 13(2) (1R,5S,6S)-2-[(2S,4S)-2-(4-Amidinopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

1500 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [pre-

pared as described in st p (1) above] were dissolved in 75 ml of a 1 : 1 by volume mixture of t trahydrofuran and water, and 2400 mg of a 10% w/w palladium-on-carbon catalyst were added to the resulting solution. The mixture was then hydrogenated in an atmosphere of hydrogen at 28°C for 1 hour. At the end of this time, the catalyst was removed by filtration, and the filtrate was washed with diethyl ether. The filtrate was then concentrated to 20 ml by evaporation under reduced pressure. The solution was then subjected to reverse phase silica gel column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque, 100 ml), eluted with mixtures of acetonitrile and water in proportions of 0 : 100, 2 : 98, 4 : 96, 6 : 94 and 8 : 92 by volume, in that order. The fractions containing the desired compound were collected, concentrated to 3 ml by evaporation under reduced pressure, and cooled to precipitate colourless needle-like crystals. The crystals were filtered off and dried to obtain 435 mg of the title compound as crystals, melting at 218 - 220°C (with decomposition).

Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

298.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1755, 1652, 1606, 1449, 1386, 1246.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.20 (3H, doublet, J = 6.8 Hz);

1.30 (3H, doublet, J = 6.3 Hz);

1.66 (1H, doubled doublet of doublets, J = 13.7, 8.8 & 5.4 Hz);

2.28 (3H, singlet);

2.74 - 2.87 (2H, multiplet);

3.09 (1H, doublet of doublets, J = 10.8 & 1.5 Hz);

3.30 - 3.90 (12H, multiplet);

4.18 - 4.31 (2H, multiplet).

Nuclear Magnetic Resonance Spectrum (¹³C, D₂O, external standard: tetramethylsilane) δ ppm:

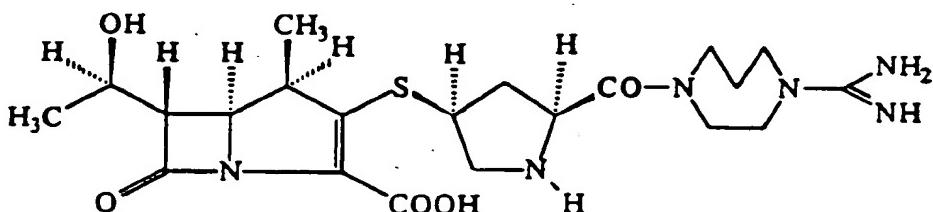
15.7, 19.9, 34.9, 39.1, 39.3, 40.9, 42.4, 43.3, 43.9, 44.5, 55.7, 58.0, 62.2, 64.9, 65.0, 131.2, 141.6, 156.3, 167.5, 171.1, 175.9.

EXAMPLE 14

30

(1R,5S,6S)-2-[(2S,4S)-2-(4-Amidinohomopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

35



40

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[4-(4-nitrobenzyloxycarbonylamidino)homopiperazin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 3) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

299.

50 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1754, 1608, 1580, 1456, 1387, 1262.

Nuclear Magnetic Resonance Spectrum (¹H, 270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.21 (3H, doublet, J = 7.2 Hz);

1.30 (3H, doublet, J = 6.3 Hz);

1.46 - 1.54 (1H, multiplet);

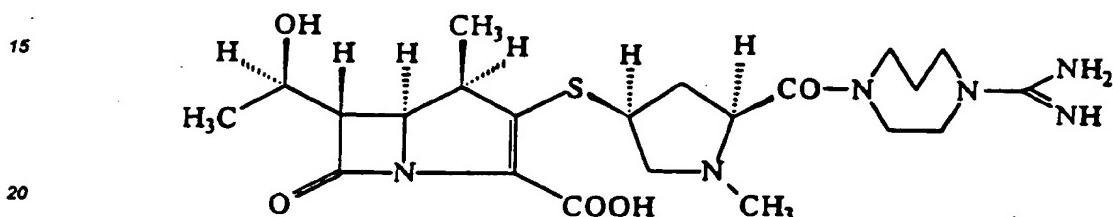
1.84 - 1.96 (2H, multiplet);

2.70 - 2.80 (1H, multiplet);

- 3.08 (1H, doublet of doublets, $J = 12.4 \& 3.3$ Hz);
 3.14 (1H, doublet of doublets, $J = 12.4 \& 5.4$ Hz);
 3.37 - 3.45 (2H, multiplet);
 3.52 - 3.95 (9H, multiplet);
 4.04 - 4.14 (1H, multiplet);
 4.20 - 4.29 (2H, multiplet).

EXAMPLE 15

(1R,5S,6S)-2-[(2S,4S)-2-(4-Amidinohomopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)homopiperazin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 4) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:
 298.

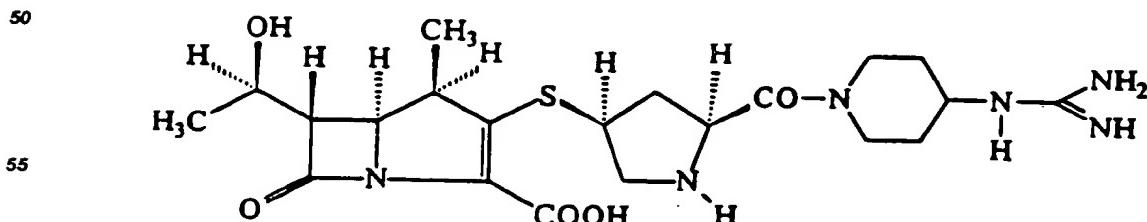
Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:
 1755, 1650, 1607, 1455, 1385, 1258.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 1.20 (3H, doublet, $J = 7.2$ Hz);
 1.30 (3H, doublet, $J = 6.3$ Hz);
 1.60 (1H, doubled doublet of doublets, $J = 13.5, 9.0 \& 5.5$ Hz);
 1.80 - 1.95 (2H, multiplet);
 2.24 & 2.25 (together 3H, two singlets);
 2.74 - 2.87 (2H, multiplet);
 3.09 (1H, doublet, $J = 9.0$ Hz);
 3.33 - 3.95 (12H, multiplet);
 4.19 (1H, doublet of doublets, $J = 9.0 \& 2.4$ Hz);
 4.22 - 4.28 (1H, multiplet).

EXAMPLE 16

(1R,5S,6S)-2-[(2S,4S)-2-(4-Guanidinopiperidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl]-1-methyl 1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2*S*,4*S*)-4-mercaptop-1-(4-nitrobenzyl xycarbonyl)-2-[4-(4-nitrobenzyloxycarbonylguanidino)piperidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 5) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

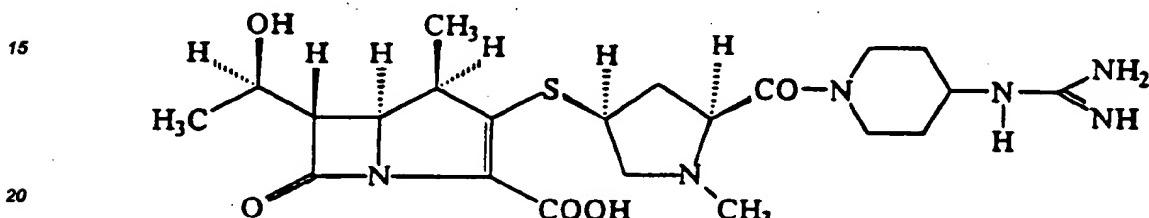
5 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

299.

EXAMPLE 17

10

(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-(4-Guanidinopiperidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl]-1-methyl 1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2*S*,4*S*)-4-mercaptop-1-methyl-2-[4-(4-nitrobenzyloxycarbonylguanidino)piperidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 6) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

25 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

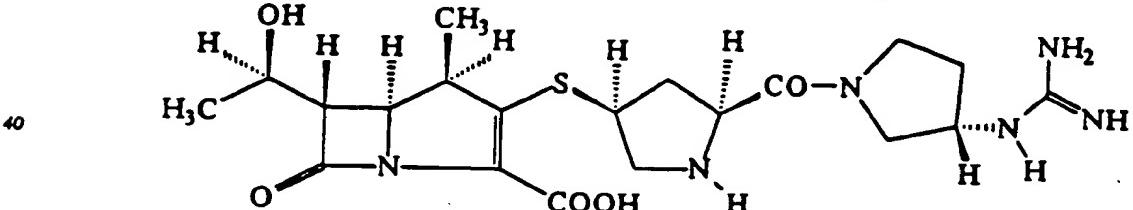
298.

30

EXAMPLE 18

(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-[(3*S*)-3-Guanidinopyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

35



45 A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl]-1-methyl 1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2*S*,4*S*)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[(3*S*)-3-(4-nitrobenzyloxy-carbonylguanidino)piperidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 7) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

50 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

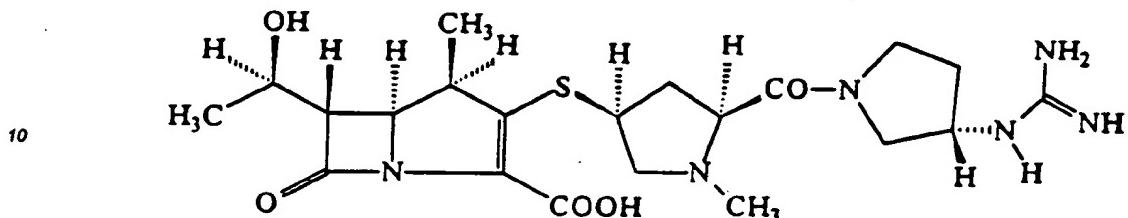
299.

55

EXAMPLE 19

(1R,5S,6S)-2-[(2S,4S)-2-[(3S)-3-Guanidinopyrrolidin-1-ylcarbonyl]-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15 A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S) 2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[(3S)-3-(4-nitrobenzyloxycarbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 8) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

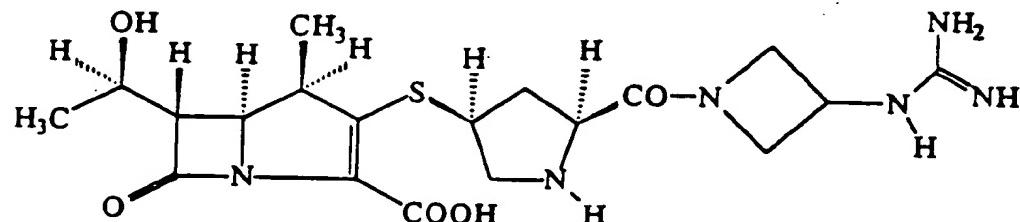
20 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:
298.

EXAMPLE 20

25 (1R,5S,6S)-2-[(2S,4S)-2-(3-Guanidinoazetidin-1-yl-carbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

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A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[3-(4-nitrobenzyloxycarbonylguanidino)azetidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 9) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:
299.

45

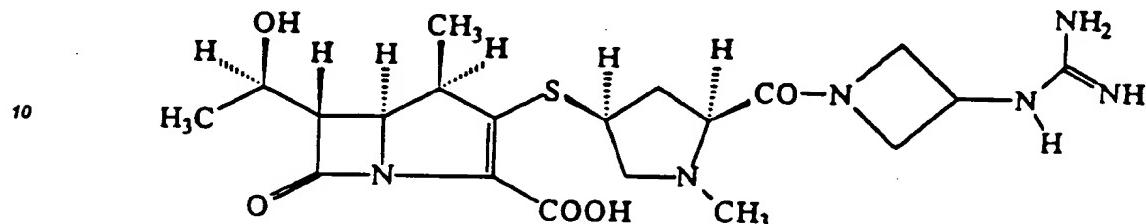
50

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EXAMPLE 21

(1R,5S,6S)-2-[(2S,4S)-2-(3-Guanidinoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5S,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[3-(4-nitrobenzyloxycarbonyl)guanidino]azetidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 10) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

20

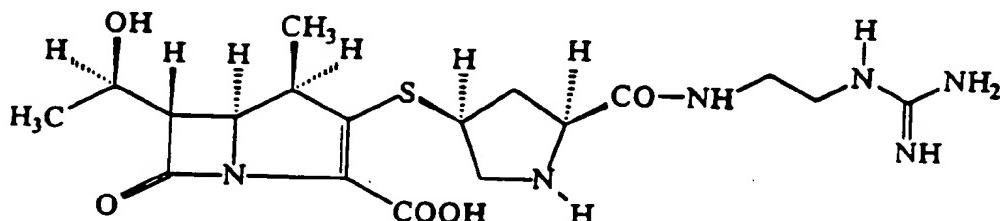
Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

298.

25

(1R,5S,6S)-2-[(2S,4S)-2-(2-Guanidinoethylcarbamoyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

30



35

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5S,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonyl)guanidino]ethylcarbamoyl]pyrrolidine (prepared as described in Preparation 11) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

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Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

299.

45

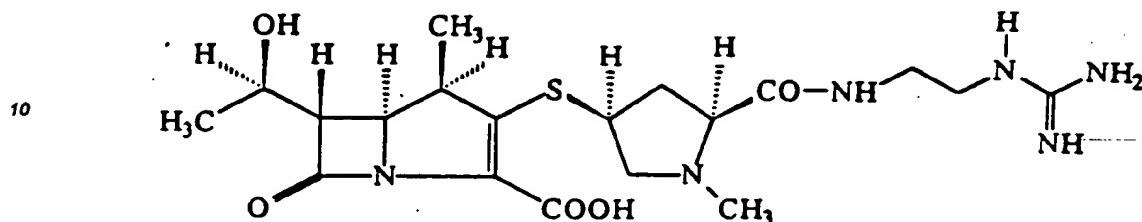
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EXAMPLE 23

(1R,5S,6S)-2-[(2S,4S)-2-(2-Guanidinoethylcarbamyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[2-(4-nitrobenzyloxycarbonylguanidino)ethylcarbamoyl]pyrrolidine (prepared as described in Preparation 12) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

20

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:
298.

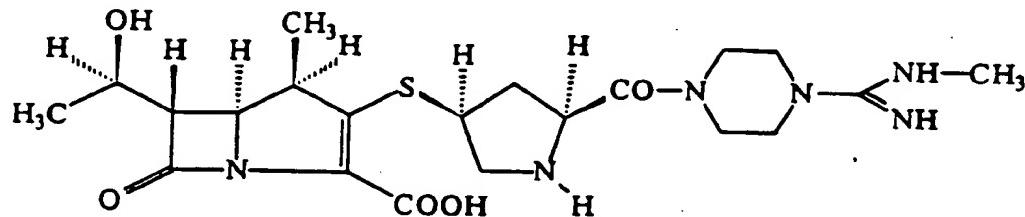
EXAMPLE 24

25

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[4-(methylamidino)piperazin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid

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A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-2-[4-(methyl-4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 13) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:
299.

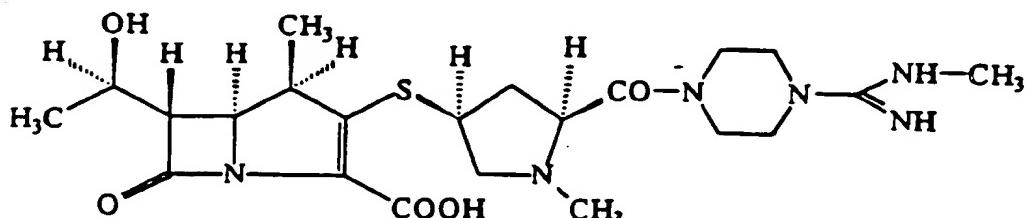
45

EXAMPLE 25

50

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-[4-(methylamidino)piperazin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylic acid

55



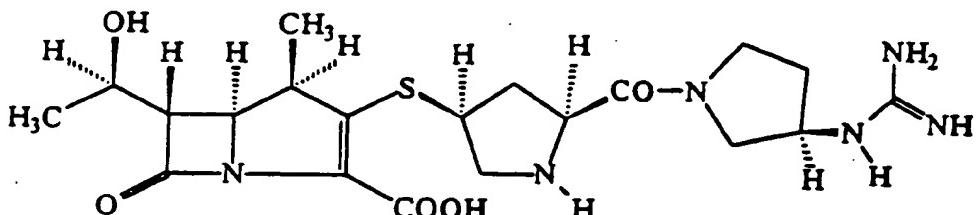
A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[4-(methyl-4-nitrobenzyloxycarbonylamido)piperazin-1-ylcarbonyl]pyrrolidin (prepared as described in Preparation 14) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

298.

EXAMPLE 26

(1R,5S,6S)-2-((2S,4S)-2-[(3R)-3-Guanidinopyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



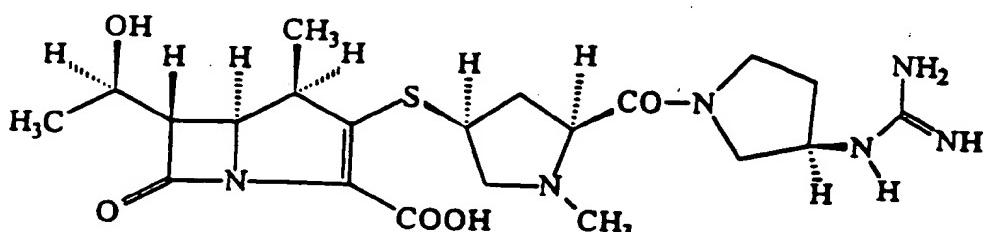
A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[(3R)-3-(4-nitrobenzyloxy-carbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 15) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

299.

EXAMPLE 27

(1R,5S,6S)-2-((2S,4S)-2-[(3R)-3-Guanidinopyrrolidin-1-ylcarbonyl]-1-methylpyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[(3R)-3-(4-nitrobenzyloxycarbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 16) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

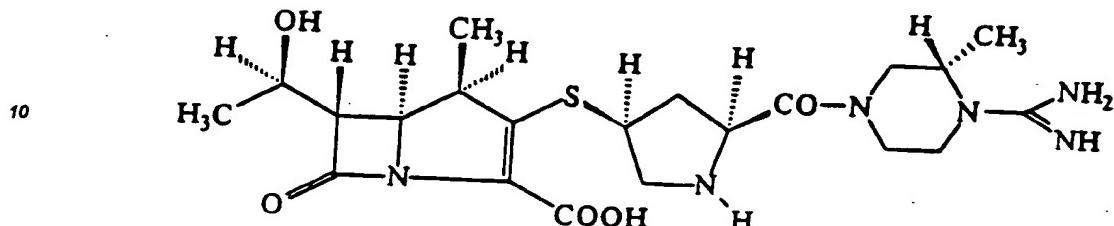
Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

298.

EXAMPLE 28

(1R,5S,6S)-2-((2S,4S)-2-[(3R)-4-Amidino-3-methylpiperazin-1-ylcarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[(3R)-4-(4-nitrobenzyloxy-carbonylamido)-3-methylpiperazin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 17) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

20

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

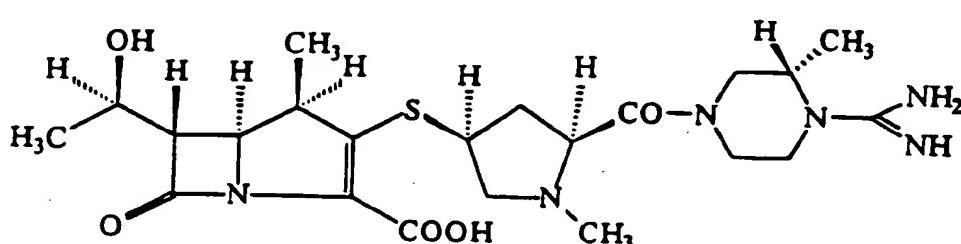
299.

25

(1R,5S,6S)-2-((2S,4S)-2-[(3R)-4-Amidino-3-methylpiperazin-1-ylcarbonyl]-1-methylpyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

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40

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-methyl-2-[(3R)-4-(4-nitrobenzyloxycarbonylamido)-3-methylpiperazin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 18) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

45

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

298.

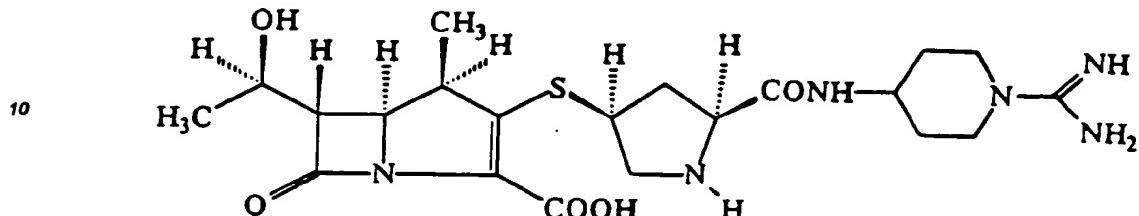
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EXAMPLE 30

(1R,5S,6S)-2-[(2S,4S)-2-[1-Amidinopiperidin-4-ylcarbamoyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[1-(4-nitrobenzyloxycarbonylamidino)piperidin-4-ylcarbamoyl]pyrrolidine (prepared as described in Preparation 19) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

20

Ultraviolet Absorption Spectrum (H_2O), λ_{\max} nm:

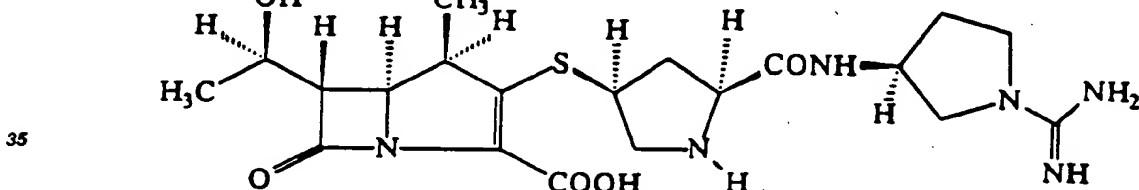
299.

EXAMPLE 31

25

(1R,5S,6S)-2-[(2S,4S)-2-[(3S)-1-Amidinopyrrolidin-3-ylcarbamoyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

30



40

A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-1-(4-nitrobenzyloxycarbonylamidino)pyrrolidin-3-ylcarbamoyl]pyrrolidine (prepared as described in Preparation 20) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

Ultraviolet Absorption Spectrum (H_2O), λ_{\max} nm:

45

299.

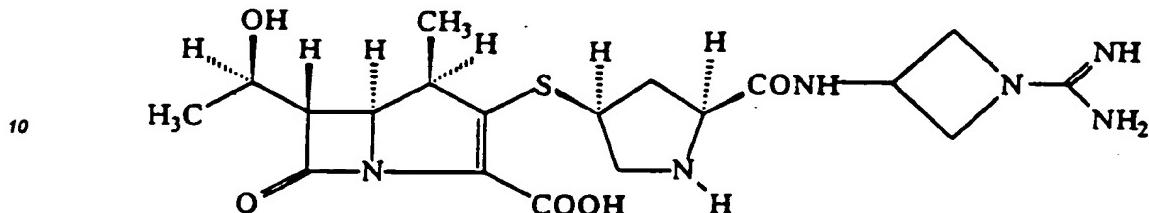
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55

EXAMPLE 32

(1R,5S,6S)-2-((2S,4S)-2-[1-Amidinoazetidin-3-ylcarbamoyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



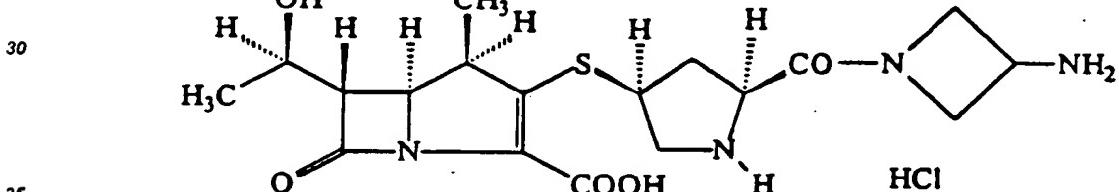
15 A procedure similar to that described in Example 13 was repeated, but using 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and (2S,4S)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)-2-[1-(4-nitrobenzyloxycarbonylamino)azetidin-3-ylcarbamoyl]pyrrolidine (prepared as described in Preparation 21) as starting materials, in relative proportions similar to those used in that Example, to obtain the title compound.

20 Ultraviolet Absorption Spectrum (H_2O), λ_{\max} nm:

299.

EXAMPLE 33

25 (1R,5S,6S)-2-((2S,4S)-2-[3-Aminoazetidin-1-ylcarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride



33(1) 4-Nitrobenzyl (1R,5S,6S)-2-((2S,4S)-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate

40

167 μl of diphenylphosphoric acid chloride and 140 μl of diisopropylethylamine were added dropwise at the same time, whilst ice-cooling, to a solution of 278 mg of 4-nitrobenzyl (1R,5R,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate in 4 ml of dry acetonitrile, and the resulting mixture was stirred at the same temperature for 1 hour. At the end of this time, a solution of 430 mg of (2S,4S)-4-mercaptop-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 22) in 4 ml of dry acetonitrile and 134 μl of diisopropylethylamine were added dropwise at the same time to the mixture, whilst ice-cooling. The resulting mixture was then stirred at the same temperature for 2 hours, after which it was left to stand overnight whilst ice-cooling. The reaction mixture was then diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride. The ethyl acetate layer was dehydrated over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, and the fractions obtained by elution with a 98 : 2 by volume mixture of ethyl acetate and methanol were combined and concentrated by evaporation under reduced pressure, to give 224 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{\max} cm^{-1} :

55 1772, 1713, 1659, 1608, 1522, 1453, 1403, 1347.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide + D_2O , 270 MHz) 8 ppm:

1.06 - 1.27 (6H, multiplet);

1.66 - 1.89 (1H, multiplet);

- 2.64 - 2.85 (1H, multiplet);
 3.08 - 3.37 (2H, multiplet);
 3.41 - 4.59 (11H, multiplet);
 5.07 - 5.52 (6H, multiplet);
 5 7.51 - 7.78 (6H, multiplet);
 8.23 (6H, doublet, J = 8.79 Hz).

33(2) (1R,5S,6S)-2-[(2S,4S)-2-(3-Aminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride

10 216 mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-4-nitrobenzyloxycarbonyl]pyrrolidin-4-ylthio)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] were dissolved in 10 ml of a 3 : 2 by volume mixture of tetrahydrofuran and water. 250 mg of a 10% w/w palladium-on-carbon catalyst and 239 μl of 1N aqueous hydrochloric acid were then added to the resulting solution, after which the mixture was hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen. At the end of this time, the catalyst was removed by filtration, and the filtrate was washed with diethyl ether. The aqueous phase was then concentrated by evaporation under reduced pressure. The resulting residue was subjected to column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque, 18 ml). Of the fractions obtained by elution with water, the one containing the title compound was concentrated by evaporation under reduced pressure and freeze-dried to give 46 mg of the title compound as a powder.

20 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

297.

25 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

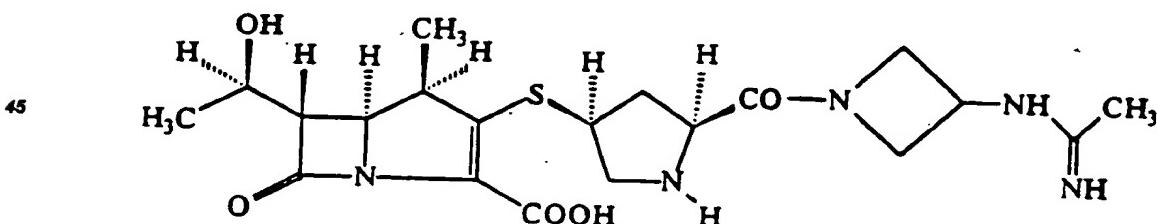
1756, 1661, 1596, 1486, 1462, 1391, 1287, 1180.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 30 1.21 (3H, doublet, J = 7.32 Hz);
 1.29 (3H, doublet, J = 6.35 Hz);
 1.95 - 2.12 (1H, multiplet);
 2.90 - 3.05 (1H, multiplet);
 3.29 - 3.51 (3H, multiplet);
 3.72 - 3.83 (1H, multiplet);
 3.97 - 4.10 (1H, multiplet);
 35 4.13 - 4.86 (8H, multiplet).

EXAMPLE 34

(1R,5S,6S)-2-[(2S,4S)-2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



50 34(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-(3-[N-(4-nitrobenzyloxycarbonyl)-N-acetimidoylamino]azetidin-1-ylcarbonyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

55 0.35 ml of diphenylphosphoric acid chloride and 0.29 ml of diisopropylethylamine were added dropwise at the same time to a solution of 0.55 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate in 10 ml of dry acetonitrile, whilst ice-cooling, and the resulting mixture was stirred at the same temperature for 50 minutes. At the end of this time, a solution of 0.82 g of (2S,4S)-4-mercapto-2-

{3-[N-(4-nitrobenzyloxycarbonyl)-N-acetimidoylamino]azetidin-1-ylcarbonyl}-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 23) in 10 ml of dry acetonitrile and 0.24 ml of diisopropylethylamine were added dropwise at the same time to the mixture, whilst ice-cooling. The resulting mixture was then stirred at the same temperature for 2 hours and then at room temperature for 1 hour. At the end of this time,

5 the reaction mixture was concentrated by evaporation under reduced pressure and the resulting residue was diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography (Silica gel 60 9385, manufactured by Merck, 200 ml), to give 0.77 g of the title compound, in the form of an amorphous powder from the fraction obtained by elution with a 95 : 5 by volume mixture of ethyl acetate and methanol.

10 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1773, 1709, 1607, 1549, 1522, 1448, 1346, 1225.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

15 1.27 & 1.28 (together 3H, two doublets, J = 7.33 Hz);

1.36 (3H, doublet, J = 6.35 Hz);

1.47 - 2.28 (3H, multiplet);

2.19 & 2.22 (together 3H, two singlets);

2.50 - 2.83 (1H, multiplet);

3.26 - 3.52 (3H, multiplet);

20 3.59 - 3.78 (1H, multiplet);

3.70 - 4.84 (9H, multiplet);

5.06 - 5.51 (6H, multiplet);

7.48 - 7.66 (6H, multiplet);

8.19 - 8.23 (6H, multiplet).

25

34(2) (1R,5S,6S)-2-[(2S,4S)-2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

30 0.77 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-(3-[N-(4-nitrobenzyloxycarbonyl)-N-acetimidoylamino]azetidin-1-ylcarbonyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] was dissolved in 15 ml of a 2 : 1 by volume mixture of tetrahydrofuran and water. 0.77 g of a 10% w/w palladium-on-carbon catalyst was then added to the resulting solution, after which the mixture was hydrogenated at room temperature for 2 hours in a hydrogen atmosphere. At the end of this time, the catalyst was removed by filtration, and the filtrate was washed with diethyl ether. The aqueous layer was then concentrated by evaporation under reduced pressure, and the resulting residue was subjected to reverse phase column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque, 100 ml). The fraction containing the title compound and obtained by elution with 4% by volume aqueous acetonitrile was concentrated by evaporation under reduced pressure and freeze-dried, to give 0.13 g of the title compound as a powder.

35 40 Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

300.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1755, 1633, 1591, 1463, 1389, 1286, 1262.

45 Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.22 (3H, doublet, J = 6.84 Hz);

1.30 (3H, doublet, J = 6.35 Hz);

1.64 - 1.74 (1H, multiplet);

2.25 - 2.35 (3H, multiplet);

50 2.58 - 2.70 (1H, multiplet);

2.98 - 3.04 (1H, multiplet);

3.20 (1H, doubled doublet of doublets, J = 12.21, 5.86 & 2.44 Hz);

3.34 - 3.45 (1H, multiplet);

3.44 (1H, doublet of doublets, J = 6.35 & 2.44 Hz);

55 3.73 - 3.88 (2H, multiplet);

4.03 - 4.10 (1H, multiplet);

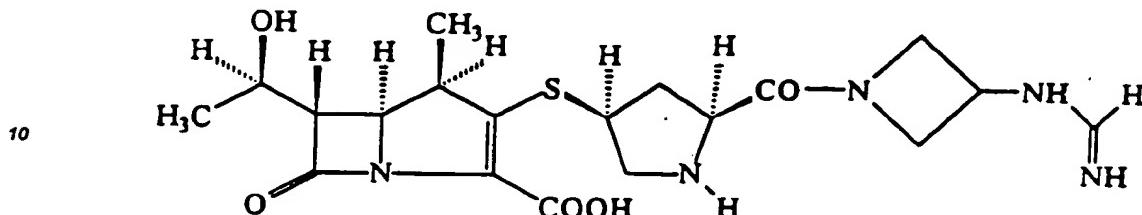
4.19 - 4.37 (3H, multiplet);

4.41 - 4.90 (3H, multiplet).

EXAMPLE 35

(1R,5S,6S)-2-[(2S,4S)-2-(3-Formimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15 A procedure similar to that described in Example 34 was repeated, but using 0.12 g of 4-nitrobenzyl (1R,5R,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate and 0.17 g of (2S,4S)-4-mercapto-2-[3-(N-4-nitrobenzyloxycarbonylformimidoylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 24), to give 19 mg of the title compound as a powder.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

20 301.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

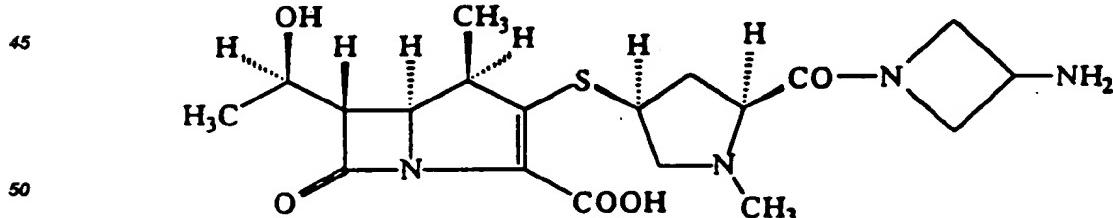
1754, 1645, 1592, 1463, 1388, 1319, 1289, 1262.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

25 1.22 (3H, doublet, $J = 7.22$ Hz);
1.30 (3H, doublet, $J = 6.33$ Hz);
1.66 - 1.76 (1H, multiplet);
2.61 - 2.75 (1H, multiplet);
3.01 - 3.13 (1H, multiplet);
30 3.20 - 3.30 (1H, multiplet);
3.35 - 3.48 (2H, multiplet);
3.76 - 3.98 (2H, multiplet);
4.04 - 4.13 (1H, multiplet);
4.20 - 4.56 (4H, multiplet);
35 4.61 - 4.88 (2H, multiplet);
7.87 & 7.88 (1H, two singlets).

EXAMPLE 36

40 (1R,5S,6S)-2-[(2S,4S)-2-(3-Aminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



45 36(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-[3-(4-nitrobenzyloxycarbonyl)amino]azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

55

A solution of 0.42 g of (2S,4S)-4-mercapto-1-methyl-2-[3-(4-nitrobenzyloxycarbonyl)amino]azetidin-1-ylcarbonyl]pyrrolidine (prepared as described in Preparation 25) in 10 ml of dry acetonitrile and 0.18 ml of diisopropylethylamine were added dropwise at the same time to a solution of 0.70 g of 4-nitrobenzyl (1R,5R,6S)-

2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylat (prepared as described in Preparation 32) in 14 ml of dry acetonitrile, whilst ice-cooling, and the resulting mixture was left to stand at the same temperature for 2 days. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure and the residue was diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography (silica gel 60 9385, manufactured by Merck, 100 ml) to give 0.25 g of the title compound, in the form of an amorphous powder, from the fractions obtained by elution with a 95 : 5 by volume mixture of acetonitrile and methanol.

10 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1771, 1723, 1641, 1608, 1522, 1455, 1347.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

1.27 & 1.28 (together 3H, two doublets, J = 7.33 & 6.84 Hz);

1.36 (3H, doublet, J = 5.86 Hz);

1.85 - 2.04 (1H, multiplet);

2.33 & 2.37 (3H, two singlets);

2.67 - 2.80 (2H, multiplet);

3.03 - 3.39 (4H, multiplet);

3.65 - 3.73 (1H, multiplet);

3.90 - 3.95 (1H, multiplet);

4.10 - 4.83 (6H, multiplet);

5.09 - 5.52 (4H, multiplet);

7.47 - 7.67 (4H, multiplet);

8.15 - 8.26 (4H, multiplet).

25

36(2) (1R,5S,6S)-2-[(2S,4S)-2-(3-Aminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

0.25 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] was dissolved in 5.5 ml of a 6 : 5 by volume mixture of tetrahydrofuran and water, and 0.25 g of a 10% w/w palladium-on-carbon catalyst was added to the resulting solution. The mixture was then hydrogenated at room temperature for 90 minutes in an atmosphere of hydrogen. At the end of this time, the catalyst was removed by filtration, and the filtrate was washed with diethyl ether. The aqueous layer was then concentrated by evaporation under reduced pressure. The resulting residue was subjected to reverse phase column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque, 25 ml). Of the fractions obtained by elution with 5% by volume aqueous acetonitrile, the one containing the title compound was concentrated by evaporation under reduced pressure and freeze-dried, to give 0.05 g of the title compound as a powder.

40 Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

301.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1755, 1641, 1598, 1462, 1386, 1284, 1255.

45 Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard; tetradeuterated sodium trimethylsilylpropionate)

1.21 (3H, doublet, J = 7.33 Hz);

1.30 (3H, doublet, J = 6.35 Hz);

1.75 - 1.85 (1H, multiplet);

2.46 & 2.47 (together 3H, two singlets);

50 2.79 - 2.89 (1H, multiplet);

2.97 - 3.07 (1H, multiplet);

3.22 - 3.53 (4H, multiplet);

3.90 - 4.06 (2H, multiplet);

4.13 - 4.29 (4H, multiplet);

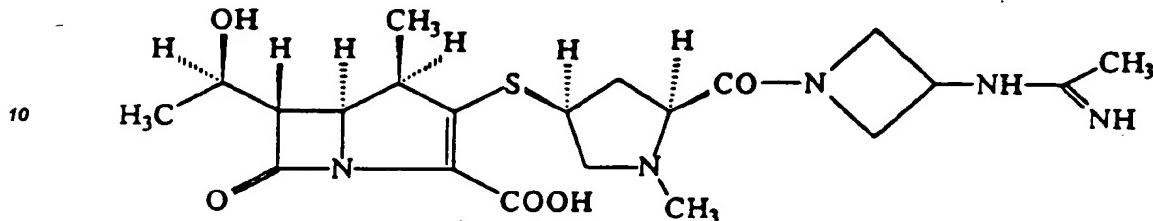
55 4.35 - 4.44 (1H, multiplet);

4.54 - 4.84 (1H, multiplet).

EXAMPLE 37

(1R,5S,6S)-2-[(2S,4S)-2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



37(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-{3-[N-(4-nitrobenzyloxycarbonyl)-N-acetimidoylamino]azetidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

20 A solution of 435 mg of (2S,4S)-4-mercaptop-1-methyl-2-{3-[N-(4-nitrobenzyloxycarbonyl)-N-acetimidoylamino]azetidin-1-ylcarbonyl}pyrrolidine (prepared as described in Preparation 26) in 4 ml of dry acetonitrile and 174 μ l of diisopropylethylamine were added dropwise at the same time to a solution of 595 mg of 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) in 10 ml of dry acetonitrile, whilst ice-cooling, and the resulting mixture was allowed to react at the same temperature for 20 minutes. It was then left to stand at room temperature for 3 hours and then in a refrigerator overnight. At the end of this time, the reaction mixture was diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was then dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography and the fractions obtained by elution with a 2 : 2 : 1 by volume mixture of methylene chloride, ethyl acetate and methanol were combined and concentrated by evaporation under reduced pressure, to give 464 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{\max} cm⁻¹:

1771, 1690, 1607, 1549, 1521, 1455, 1378, 1346.

35 Nuclear Magnetic Resonance Spectrum (270MHz, DMSO-d₆ + D₂O) δ ppm:

1.16 (6H, doublet, $J = 6.83$ Hz);
 1.59 - 1.74 (1H, multiplet);
 2.11 (3H, singlet);
 2.29 (3H, broad singlet);
 2.54 - 3.19 (3H, multiplet);
 3.27 (1H, doublet of doublets, $J = 6.35$ & 2.44 Hz);
 3.32 - 4.27 (8H, multiplet);
 4.42 - 4.60 (2H, multiplet);
 5.11 - 5.49 (4H, multiplet);
 7.60 & 7.61 (together 2H, two doublets, $J = 8.79$ Hz);
 7.70 & 7.72 (together 2H, two doublets, $J = 8.79$ Hz);
 8.16 - 8.28 (4H, multiplet).

50 37(2) (1R,5S,6S)-2-[(2S,4S)-2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

55 453 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-methyl-2-{3-[N-(4-nitrobenzyloxycarbonyl)-N-acetimidoylamino]azetidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] were dissolved in 21 ml of a 2 : 1 by volume mixture of tetrahydrofuran and water, and 500 mg of a 10% w/w palladium-on-carbon catalyst were added to the resulting solution. The mixture was then hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen. The catalyst was then removed by filtration, and the filtrate was washed with diethyl ether. The aqueous layer was concentrated by evaporation under reduced pressure. The residue was subjected to reverse phase column

chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesqu , 40 ml). Of the fractions obtained by elution with 8% by volume aqueous acetonitrile, the one containing the title compound was concentrated by evaporation under reduced pressure and freeze-dried, to give 166 mg of the title compound as a powder.

Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

5 301.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1757, 1633, 1592, 1462, 1386, 1335, 1284, 1256.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

10 1.21 (3H, doublet, J = 6.83 Hz);

1.30 (3H, doublet, J = 6.35 Hz);

1.64 - 1.78 (1H, multiplet);

2.27 (3H, singlet);

2.29 (3H, singlet);

15 2.63 - 2.85 (2H, multiplet);

3.01 - 3.21 (2H, multiplet);

3.27 - 3.46 (2H, multiplet);

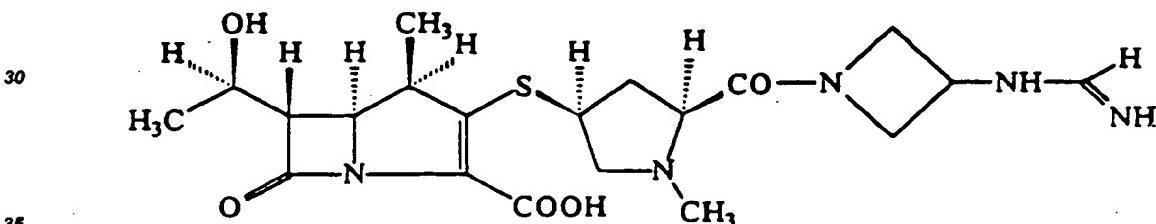
3.75 - 3.88 (1H, multiplet);

4.00 - 4.10 (1H, multiplet);

20 4.15 - 4.96 (6H, multiplet).

EXAMPLE 38

25 (1R,5S,6S)-2-[(2S,4S)-2-(3-Formimidoylaminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



30 A procedure similar to that described in Example 37 was repeated, but using 0.35 g of 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and 0.22 g of (2S,4S)-4-mercaptop-1-methyl-2-(3-[N-(4-nitrobenzyl)oxycarbonyl]-N-formimidoylamino)azetidin-1-ylcarbonyl)pyrrolidine (prepared as described in Preparation 27), to give 17 mg of the title compound as a powder.

40 Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

302.

45

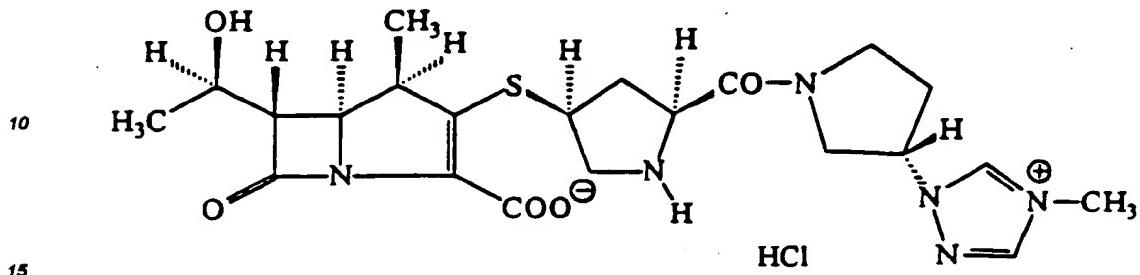
50

55

EXAMPLE 39

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3S)-3-(4-methyl-1-1,2,4-triazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

5



15

39(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-3-(1-1,2,4-triazoly)-1-pyrrolidinylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

20 486 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 5 ml of dry acetonitrile, and 379 mg of diphenylphosphoryl chloride and 182 mg of diisopropylethylamine were added dropwise, with ice-cooling, to the resulting solution. The mixture was then stirred at the same temperature for 1 hour. At the end of this time, a solution of 173 mg of diisopropylethylamine and 690 mg of (2S,4S)-4-mercapto-2-[(3S)-3-(1-1,2,4-triazoly)-1-pyrrolidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 28) in 4 ml of dry acetonitrile was added dropwise with ice-cooling, to the resulting mixture, and the mixture was stirred at the same temperature for 6 hours. The solvent was then removed by distillation under reduced pressure, and the resulting residue was dissolved in ethyl acetate. The resulting solution was then washed with water, with an aqueous solution of sodium hydrogencarbonate, again with water and finally with a saturated aqueous solution of sodium chloride. The aqueous layer was extracted with methylene chloride, and the aqueous layer was combined with the washings and dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography, using a 5 : 1 by volume mixture of ethyl acetate and methanol as the eluent, to obtain 744 mg of the title compound, as a powder.

25 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

30 1772, 1709, 1655, 1607, 1522, 1346, 854, 738.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide + D₂O) δ ppm:

35 1.50 - 1.80 (1H, multiplet);
2.20 - 2.50 (2H, multiplet);
2.70 - 2.95 (2H, multiplet);
40 3.10 - 4.30 (12H, multiplet);
4.45 - 4.75 (1H, multiplet);
5.00 - 5.50 (4H, multiplet);
7.45 - 7.78 (4H, multiplet);
7.80 - 8.00 (1H, multiplet);
45 8.15 - 8.28 (4H, multiplet);
8.50 - 8.60 (1H, multiplet).

39(2) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[(3S)-3-(4-methyl-1-1,2,4-triazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

50

528 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-3-(1-1,2,4-triazoly)-1-pyrrolidinylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] were dissolved in 6 ml of dry acetonitrile, and 121 mg of methyl trifluoromethanesulphonate were added to the resulting solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 30 minutes. The powdery product obtained by evaporation of the solvent was dissolved in a mixture of 7 ml of tetrahydrofuran and 5 ml of water, after which the mixture was hydrogenated at room temperature for 1 hour in the presence of 1 g of a 10% w/w palladium-on-carbon catalyst. At the end of this time, the catalyst was removed by filtration and the tetrahydrofuran was distilled off under reduced

pressure. The aqueous layer was then washed with diethyl ether and concentrated by evaporation under reduced pressure, after which it was subjected to ion exchange column chromatography (Dowex 1-X4, 50 to 100 mesh, C1 FORM, manufactured by Dow Chemical), using water as the eluent. The fractions containing the title compound were collected and concentrated to 1.5 ml by evaporation under reduced pressure.

The concentrated aqueous solution was applied to a column (Cosmosil 75C₁₈-prep, manufactured by Nacalai) and eluted with water. The fractions containing the title compound were combined, concentrated by evaporation under reduced pressure and freeze-dried, to obtain 85 mg of the title compound as a colourless powder. Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

296.7.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

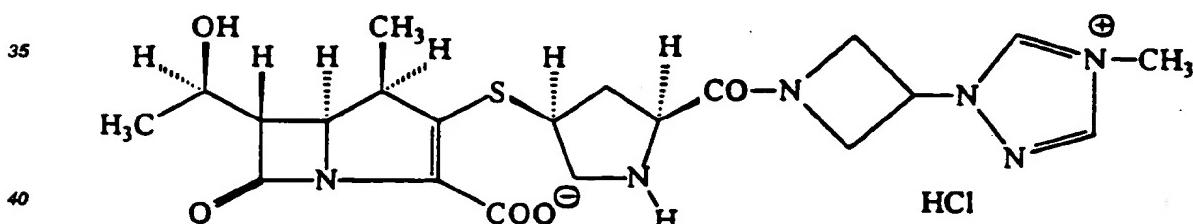
3394, 1758, 1655, 1586, 1460, 1373.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, Internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.18 - 1.23 (3H,m), 1.27-1.30 (3H, multiplet);
 1.95 - 2.11 (1H, multiplet);
 2.40 - 2.80 (2H, multiplet);
 2.95 - 3.20 (1H, multiplet);
 3.30 - 3.40 (1H, multiplet);
 3.40 - 3.54 (2H, multiplet);
 3.70 - 3.85 (2H, multiplet);
 3.85 - 4.05 (3H, multiplet);
 4.05 - 4.15 (3H, multiplet);
 4.15 - 4.30 (2H, multiplet);
 4.70 - 4.85 (2H, multiplet);
 5.45 - 5.60 (1H, multiplet);
 8.84 & 8.87 (together 1H, two singlets)

EXAMPLE 40

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[3-(4-methyl-1-1,2,4-triazolio)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride



40(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[3-(1-1,2,4-triazoly)-1-azetidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate

886 mg of 4-nitrobenzyl (1R,5S,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) was dissolved in 10 ml of dry acetonitrile, and 0.26 ml of diisopropylethylamine and 873 mg of (2S,4S)-4-mercapto-2-[3-(1-1,2,4-triazoly)-1-azetidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (prepared as described in Preparation 29) dissolved in 5 ml of acetonitrile were added dropwise at the same time to the resulting solution, whilst ice-cooling. The mixture was then stirred at the same temperature for 3 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was diluted with ethyl acetate. The resulting mixture was washed with water, with an aqueous solution of sodium hydrogencarbonate, with water and with a saturated aqueous solution of sodium chloride. The aqueous layer was dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The residue was purified by silica gel column chromatography, using a gradient elution method, with mixtures of ethyl acetate and methanol ranging from 6 : 1 to 4 : 1 by volume as the eluent, to obtain 661 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

3402, 1709, 1665, 1608, 854, 738.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide) δ ppm:

- 5 1.10 - 1.30 (6H, multiplet);
- 1.75 - 1.90 (1H, multiplet);
- 10 2.70 - 2.85 (1H, multiplet);
- 3.55 - 3.65 (1H, multiplet);
- 3.20 - 5.10 (12H, multiplet);
- 5.15 - 5.55 (5H, multiplet);
- 7.55 - 7.80 (4H, multiplet);
- 15 7.95 - 8.10 (1H, multiplet);
- 8.20 - 8.30 (4H, multiplet);
- 8.55 - 8.75 (1H, multiplet).

40(2) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[3-(4-methyl-1-1,2,4-triazolio)azetidin-1-yl-carbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

660 mg of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[3-(1-1,2,4-triazoly)-1-azetidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] were dissolved in 7 ml of dry acetonitrile, and 154 mg of methyl trifluoromethanesulphonate were added to the resulting solution, whilst ice-cooling. The mixture was then stirred at the same temperature for 30 minutes. At the end of this time, the powdery product obtained by evaporation of the solvent under reduced pressure was dissolved in a mixture of 14 ml of tetrahydrofuran and 14 ml of water, and the mixture was hydrogenated at room temperature for 1 hour in the presence of 1.6 g of a 10% w/w palladium-on-carbon catalyst and in an atmosphere of hydrogen. The catalyst was removed by filtration and the tetrahydrofuran was removed by distillation under reduced pressure, after which the aqueous layer was washed with diethyl ether. The aqueous layer was then concentrated by evaporation under reduced pressure, and then subjected to ion exchange column chromatography (Dowex 1-X4, 50 to 100 mesh, C1 FORM, manufactured by Dow Chemical) using water as the eluent. The fractions containing the title compound were collected and concentrated by evaporation under reduced pressure.

30 The aqueous solution was applied to a column (Cosmosil 75C₁₈-prep, manufactured by Nacalai) and eluted with water. The fractions containing the title compound were combined, concentrated by evaporation under reduced pressure and freeze-dried, to obtain 139 mg of the title compound as a colourless powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

3390, 1759, 1664, 1586, 1455, 1369.

35 Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

- 1.21 (3H, doublet, J = 5.99 Hz);
- 1.29 (3H, doublet, J = 6.29 Hz);
- 1.80 - 2.20 (2H, multiplet);
- 2.90 - 3.10 (1H, multiplet);
- 3.30 - 3.40 (1H, multiplet);
- 3.40 - 3.50 (1H, multiplet);
- 3.75 - 3.80 (1H, multiplet);
- 4.20 - 4.30 (2H, multiplet);
- 3.90 - 5.20 (8H, multiplet);
- 5.45 - 5.65 (1H, multiplet);
- 5.70 - 5.80 (1H, multiplet);
- 8.96 & 8.97 (together 1H, two singlets).

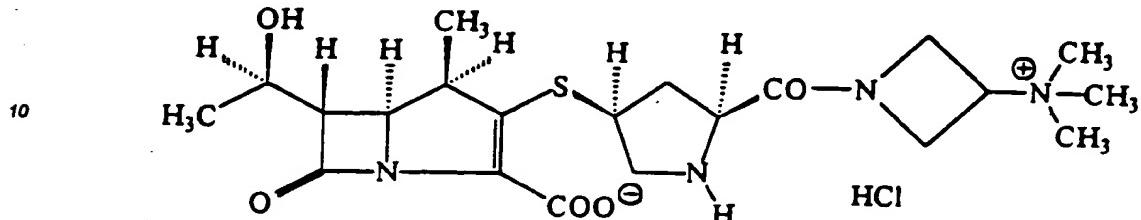
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EXAMPLE 41

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-(3-trimethylammonioazetidin-1-ylcarbonyl)-pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

5



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41(1) 4-Nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate

A solution of 0.98 g of (2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 30) dissolved in 20 ml of dry acetonitrile and 0.418 ml of diisopropylethylamine were added dropwise at the same time, whilst ice-cooling, to a solution of 1.43 g of 4-nitrobenzyl (1R,5S,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) in 25 ml of dry acetonitrile. The mixture was then stirred at the same temperature for 2 hours, after which it was left to stand in a refrigerator overnight. The reaction mixture was then concentrated by evaporation under reduced pressure, and the resulting residue was diluted with ethyl acetate; the resulting mixture was washed with water and then with an aqueous solution of sodium chloride. The ethyl acetate layer was dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The residue was purified by silica gel column chromatography and the fractions obtained by elution with a 75 : 25 by volume mixture of ethyl acetate and methanol were combined and concentrated by evaporation under reduced pressure, to obtain 1.16 g of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1774, 1712, 1663, 1607, 1522, 1456, 1404, 1346.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

1.26 (3H, doublet, J = 7.11 Hz);
 1.36 (3H, doublet, J = 6.13 Hz);
 2.00 - 2.18 (1H, multiplet);
 2.10, 2.14, 2.25 & 2.28 (together 6H, four singlets);
 2.51 - 2.73 (1H, multiplet);
 2.86 - 4.56 (13H, multiplet);
 5.08 - 5.54 (4H, multiplet);
 7.50 (2H, doublet, J = 8.57 Hz);
 7.65 (2H, doublet, J = 8.57 Hz);
 8.23 (4H, doublet, J = 8.57 Hz).

45

41(2) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-(3-trimethylammonioazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride

1.00 g of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] was dissolved in 12 ml of dry acetonitrile, and 243 mg of methyl trifluoromethanesulphonate were added to the resulting solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting powdery product was dissolved in a mixture of 20 ml of tetrahydrofuran and 20 ml of water. The mixture was then hydrogenated at room temperature for 2 hours in the presence of 1.00 g of a 10% w/w palladium-on-carbon catalyst and in an atmosphere of hydrogen. The catalyst was then removed by filtration, the filtrate was washed with diethyl ether. The resulting aqueous phase was concentrated by evaporation under reduced pressure. The residue was subjected to ion exchange column chromatography

(Dexx 1-X4, 50 to 100 mesh, C1⁻ model, manufactured by Dow Chemical) using water as the eluent. The fraction containing the title compound was concentrated by evaporation under reduced pressure and subjected to reverse phase column chromatography (Cosmosil 75C₁₈-prep, manufactured by Nacalai Tesque) and eluted with water. The fractions containing the title compound were concentrated by evaporation under reduced pressure and freeze-dried, to obtain 265 mg of the title compound as a powder.

Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

296.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1758, 1665, 1594, 1482, 1373, 1285, 1255, 1145.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.21 (3H, doublet, J = 7.17 Hz);

1.28 (3H, doublet, J = 6.29 Hz);

1.98 - 2.09 (1H, multiplet);

2.93 - 3.05 (1H, multiplet);

3.21 & 3.22 (together 9H, two singlets);

3.32 - 3.50 (3H, multiplet);

3.78 (1H, doublet of doublets, J = 12.26 & 6.60 Hz);

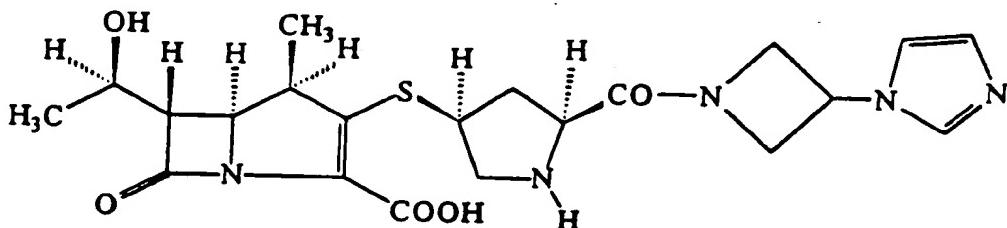
4.01 - 4.12 (1H, multiplet);

4.20 - 4.29 (2H, multiplet);

4.43 - 4.85 (6H, multiplet).

EXAMPLE 42

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(2S,4S)-2-[3-(1-imidazolyl)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid



42(1) 4-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[3-(1-imidazolyl)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate

A solution of 3.10 g of (2S,4S)-2-[3-(1-imidazolyl)azetidin-1-ylcarbonyl]-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (prepared as described in Preparation 31) dissolved in 25 ml of dry acetonitrile and 1.25 ml of diisopropylethylamine were added dropwise at the same time, whilst ice-cooling, to a solution of 4.27 g of 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) in 55 ml of dry acetonitrile. The resulting mixture was left to stand at the same temperature for 1 hour and then in an refrigerator overnight. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the resulting residue was diluted with ethyl acetate. The mixture thus obtained was washed with water and then with an aqueous solution of sodium chloride. The resulting ethyl acetate solution was dried over anhydrous magnesium sulphate and then concentrated by evaporation under reduced pressure. The residue was applied to a silica gel chromatography column, and the fractions obtained by elution with a 7 : 7 : 6 by volume mixture of methylene chloride, ethyl acetate and methanol were combined and concentrated by evaporation under reduced pressure, to obtain 2.94 g of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1772, 1708, 1667, 1607, 1522, 1449, 1403, 1346, 1209.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

1.27 (3H, doublet, J = 7.19 Hz);

1.36 (3H, doublet, J = 6.14 Hz);

2.15 - 5.55 (19H, multiplet);
 7.10 - 8.28 (11H, multiplet).

42(2) (1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(2S,4S)-2-[3-(1-imidazoly)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid

0.25 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[3-(1-imidazoly)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in step (1) above] was dissolved in a mixture of 7.5 ml of tetrahydrofuran and 7.5 ml of water, and 10 0.25 g of a 10% w/w palladium-on-carbon catalyst was added to the resulting solution, after which the mixture was hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen. At the end of this time, the catalyst was removed by filtration and the filtrate was washed with diethyl ether. The resulting aqueous layer was then concentrated by evaporation under reduced pressure, and the residue was subjected to reverse phase column chromatography (Cosmosil 75C₁₈-prep, 30 g, manufactured by Nacalai Tesque). Of the fractions 15 obtained by elution with 7% by volume aqueous acetonitrile, the fraction containing the title compound was concentrated by evaporation under reduced pressure and freeze-dried, to obtain 70 mg of the title compound as a powder.

Ultraviolet Absorption Spectrum (H₂O), λ_{max} nm:

297.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

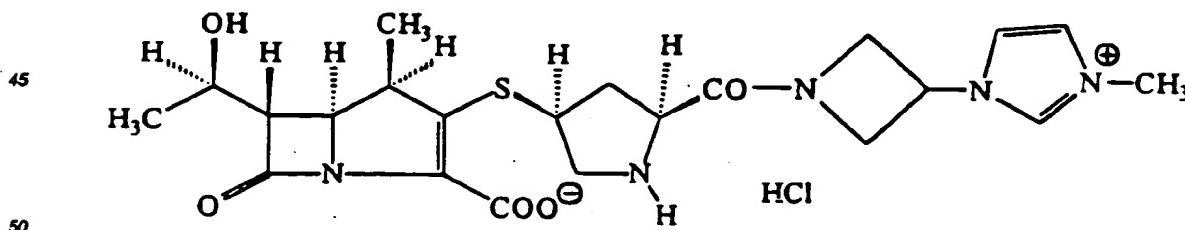
1757, 1660, 1598, 1466, 1383, 1285, 1255, 1181, 1149.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.22 (3H, doublet, J = 7.12 Hz);
 1.30 (3H, doublet, J = 6.27 Hz);
 1.90 - 2.02 (1H, multiplet);
 2.84 - 2.95 (1H, multiplet);
 3.29 - 3.50 (3H, multiplet);
 3.56 - 3.65 (1H, multiplet);
 3.91 - 4.03 (1H, multiplet);
 4.20 - 4.43 (4H, multiplet);
 4.50 - 5.45 (4H, multiplet);
 7.22 & 7.23 (together 1H, two singlets);
 7.54 (1H, singlet);
 8.12 (1H, singlet).

EXAMPLE 43

(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-1-methyl-2-[(2S,4S)-2-[3-(3-methyl-1-imidazolio)azetidin-1-ylcarbonyl]pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate hydrochloride



55 1.72 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-[3-(1-imidazoly)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 42(1)] were dissolved in 18 ml of dry acetone, and 0.28 ml of methyl trifluoromethanesulphonate was added to the resulting solution, whilst ice-cooling. The mixture was then stirred at the same temperature for 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, and the powdery product thus obtained was dissolved in a mixture of 30 ml of tetrahydrofuran and 30 ml of water. The mixture was then hydrogenated at room temperature for 2 hours in the presence of 2.10 g

of a 10% w/w palladium-on-carbon catalyst and in an atmosphere of hydrogen. The reaction mixture was then treated, purified and freeze-dried in the same manner as described in Example 40(2), to obtain 383 mg of the title compound as a colourless powder.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

5 296.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1759, 1664, 1597, 1561, 1466, 1373, 1284, 1184, 1147.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

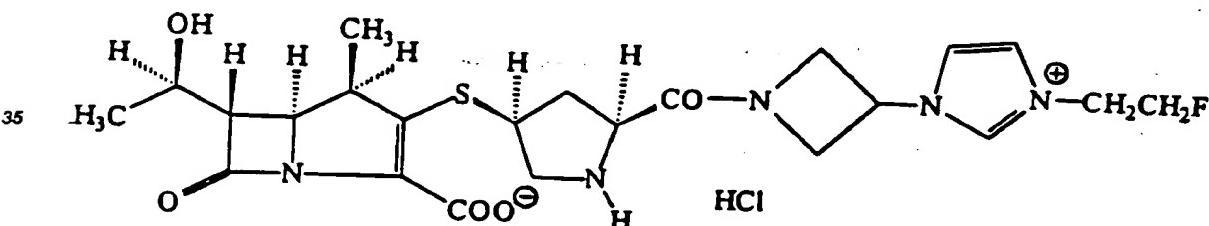
10 1.21 (3H, doublet, $J = 7.21$ Hz);
1.29 (3H, doublet, $J = 6.38$ Hz);
2.00 - 2.14 (1H, multiplet);
2.93 - 3.05 (1H, multiplet);
3.30 - 3.51 (3H, multiplet);
15 3.73 - 3.82 (1H, multiplet);
3.92 (3H, singlet);
4.01 - 4.10 (1H, multiplet);
4.20 - 4.30 (2H, multiplet);
4.38 - 4.47 (1H, multiplet);
20 4.55 - 4.96 (4H, multiplet);
5.45 - 5.55 (1H, multiplet);
7.55 (1H, singlet);
7.80 (1H, singlet);
9.00, 9.02 (1H, two singlets).

25

EXAMPLE 44

(1R,5S,6S)-2-[(2S,4S)-2-{3-[3-(2-Fluoroethyl)-1-imidazolyl]azetidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

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0.87 g of 4-nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(2S,4S)-2-{3-(1-imidazolyl)azetidin-1-ylcarbonyl}-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 42(1)] were dissolved in 10 ml of dry acetonitrile, and 0.63 ml of 1-bromo-2-fluoroethane, 0.84 g of sodium iodide and 80 ml of sodium carbonate were added to the resulting solution, after which the mixture was heated under reflux for 14 hours. At the end of this time, insolubles were filtered off and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was washed by repeated decantation with, in turn, methylene chloride and diethyl ether. It was then dried by evaporation under reduced pressure to obtain 0.494 g of a powder. The whole of this compound was dissolved in a mixture of 12.5 ml of tetrahydrofuran and 12.5 ml of water. 0.48 g of a 10% w/w palladium-on-carbon catalyst was then added to the solution, after which the mixture was hydrogenated at room temperature for 1 hour. At the end of this time, the reaction mixture was treated, purified and freeze-dried in the same manner as described in Example 40(2) to obtain 42 mg of the title compound as a colourless powder.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

297.

55 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1759, 1664, 1597, 1563, 1467, 1374, 1284, 1222, 1183.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

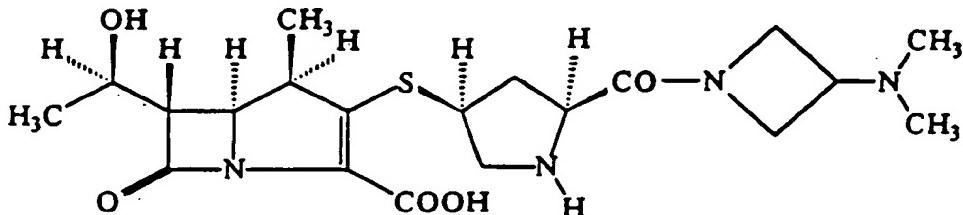
1.21 (3H, doublet, $J = 6.97$ Hz);
 1.28 (3H, doublet, $J = 6.28$ Hz);
 2.02 - 2.14 (1H, multiplet);
 2.93 - 3.07 (1H, multiplet);
 5 3.31 - 3.51 (3H, multiplet);
 3.74 - 3.83 (1H, multiplet);
 4.02 - 4.10 (1H, multiplet);
 4.20 - 4.30 (2H, multiplet);
 4.41 - 4.49 (1H, multiplet);
 10 4.54 - 4.98 (9H, multiplet);
 5.48 - 5.59 (1H, multiplet);
 7.68 (1H, singlet);
 7.88 (1H, singlet);
 9.15 & 9.17 (1H, two singlets).

15

EXAMPLE 45

(1R,5S,6S)-2-[(2S,4S)-2-(3-Dimethylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

20



25

30 0.75 g of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-1-(4-nitrobenzylloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 41(1)] was dissolved in a mixture of 21 ml of tetrahydrofuran and 14 ml of water, and 0.75 g of a 10% w/w palladium-on-carbon catalyst was added to the resulting solution, after which the mixture was hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen. At the end of this time, the catalyst was removed by filtration and the filtrate was washed with diethyl ether. The resulting aqueous solution was then concentrated by evaporation under reduced pressure, after which the residue was subjected to reverse phase column chromatography (Cosmosil 75C₁₈-prep, 25 g, manufactured by Nacalai Tesque). Of the fractions obtained by elution with 7% by volume aqueous acetonitrile, the fraction containing the title compound was concentrated by evaporation under reduced pressure and freeze-dried, to obtain 171 mg of the title compound as a powder.

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40 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

299.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1757, 1653, 1599, 1462, 1385, 1284, 1259, 1150.

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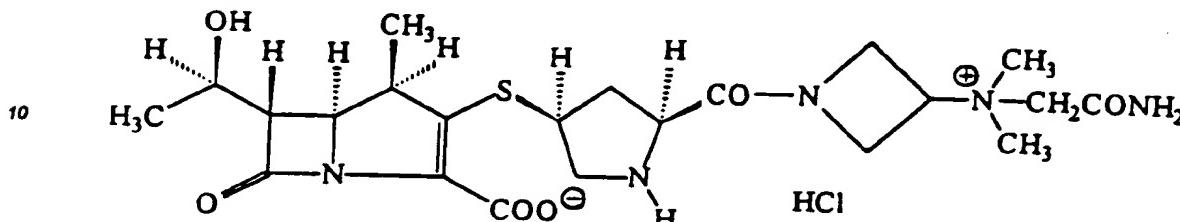
Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.22 (3H, doublet, $J = 7.22$ Hz);
 1.30 (3H, doublet, $J = 6.40$ Hz);
 1.83 - 1.92 (1H, multiplet);
 2.41 (3H, singlet);
 2.45 (3H, singlet);
 2.78 - 2.89 (1H, multiplet);
 3.26 (1H, doublet of doublets, $J = 12.14$ & 4.90 Hz);
 3.34 - 3.73 (4H, multiplet);
 3.89 - 4.06 (2H, multiplet);
 4.19 - 4.33 (5H, multiplet);
 4.43 - 4.54 (1H, multiplet).

EXAMPLE 46

(1R,5S,6S)-2-[(2S,4S)-2-(3-[N-(Carbamoylmethyl)-N,N-dimethylammonium]azetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

5



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0.60 g of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-1-(4-nitrobenzylloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 41(1)] was dissolved in 8 ml of dry acetonitrile, and 0.74 g of 2-iodoacetamide was added to the resulting solution, after which the mixture was stirred at 70°C for 2 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting residue was washed by repeated decantation, in turn, with methylene chloride and with diethyl ether. It was then dried by evaporation under reduced pressure to obtain 0.90 g of a powder. The whole of this compound was dissolved in a mixture of 24 ml of tetrahydrofuran and 16 ml of water. 0.95 g of a 10% w/w palladium-on-carbon catalyst was then added to the solution, after which the mixture was hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen.

The reaction mixture was then treated, purified and freeze-dried in the same manner as described in Example 40(2), to obtain 156 mg of the title compound as a colourless powder.

Ultraviolet Absorption Spectrum (H_2O), λ_{\max} nm:

297.

Infrared Absorption Spectrum (KBr), ν_{\max} cm⁻¹:

1767, 1701, 1607, 1521, 1445, 1404, 1346, 1170.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.21 (3H, doublet, $J = 7.18$ Hz);

1.29 (3H, doublet, $J = 6.37$ Hz);

1.98 - 2.10 (1H, multiplet);

2.93 - 3.04 (1H, multiplet);

3.38 & 3.40 (together 6H, two singlets);

3.30 - 3.50 (3H, multiplet);

3.74 - 3.80 (1H, multiplet);

4.01 - 4.10 (1H, multiplet);

4.15 - 4.30 (4H, multiplet);

4.43 - 4.88 (5H, multiplet);

4.94 - 5.03 (1H, multiplet).

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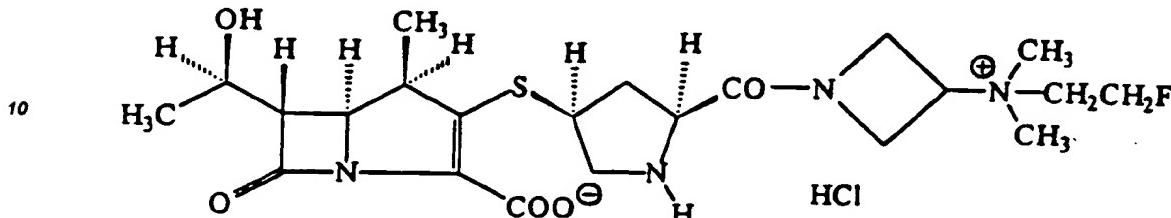
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EXAMPLE 47

(1R,5S,6S)-2-[(2S,4S)-2-{3-[(2-Fluoroethyl)dimethylammonio]azetidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

5



15

715 mg of 4-nitrobenzyl (1R,5S,6S)-2-[(2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-1-(4-nitrobenzyl)oxycarbonyl]pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 41(1)] were dissolved in 7 ml of dry acetonitrile, and 1.22 g of 1-bromo-2-fluoroethane, 721 mg of sodium iodide and 67 mg of sodium carbonate were added to the resulting solution, after which the mixture was heated under reflux for 23 hours. At the end of this time, insolubles were filtered off and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was washed by repeated decantation, in turn, with methylene chloride and ethyl diethyl ether, and the mixture was dried by evaporation under reduced pressure to obtain 400 mg of a powder. The whole of this compound was dissolved in a mixture of 8 ml of tetrahydrofuran and 8 ml of water. 0.40 g of a 10% w/w palladium-on-carbon catalyst was added to the solution, after which the mixture was hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen. The reaction mixture was then treated, purified and freeze-dried in the same manner as described in Example 40(2), to obtain 39 mg of the title compound as a colourless powder.

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

296.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1759, 1668, 1598, 1476, 1374, 1285, 1226, 1180.

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

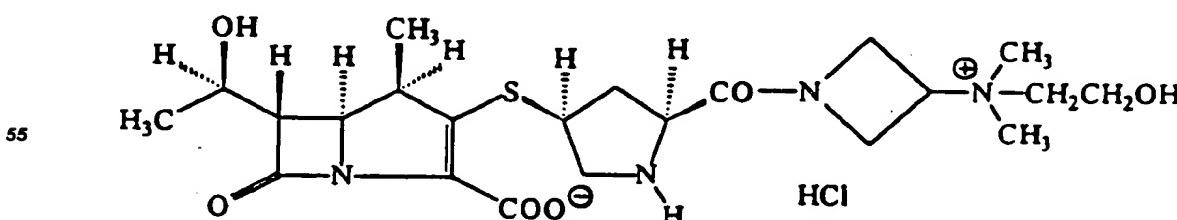
- 35 1.21 (3H, doublet, $J = 7.18$ Hz);
- 35 1.28 (3H, doublet, $J = 6.26$ Hz);
- 35 1.98 - 2.10 (1H, multiplet);
- 35 2.93 - 3.04 (1H, multiplet);
- 35 3.27 & 3.29 (together 6H, two singlets);
- 35 3.33 - 3.51 (3H, multiplet);
- 40 3.75 - 3.92 (3H, multiplet);
- 40 4.02 - 4.11 (1H, multiplet);
- 40 4.20 - 4.28 (2H, multiplet);
- 40 4.43 - 4.85 (6H, multiplet);
- 40 4.90 - 5.06 (2H, multiplet).

45

EXAMPLE 48

(1R,5S,6S)-2-[(2S,4S)-2-{3-[(2-Hydroxyethyl)dimethylammonio]azetidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride

50



5 0.65 g of 4-nitrobenzyl (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 41(1)] was dissolved in 7 ml of dry acetonitrile, and 1.05 g of 2-iodoethanol were added to the resulting solution. The mixture was then heated under reflux for 5 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was washed by repeated decantation, in turn, with methylene chloride and with diethyl ether. The mixture was then dried by evaporation under reduced pressure to obtain 0.84 g of a powder. The whole of this compound was dissolved in a mixture of 21 ml of tetrahydrofuran and 14 ml of water. 0.90 g of a 10% w/w palladium-on-carbon catalyst was then added to the solution, after which the mixture was hydrogenated at room temperature for 1.5 hours in an atmosphere of hydrogen. The reaction mixture was then treated, purified and freeze-dried in the same manner as described in Example 40(2), to obtain 55 mg of the title compound as a colourless powder.

10 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

297.

15 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1758, 1665, 1595, 1477, 1374, 1261, 1227, 1149.

20 Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) 8 ppm:

1.21 (3H, doublet, $J = 7.20$ Hz);

1.28 (3H, doublet, $J = 6.36$ Hz);

2.93 - 2.10 (1H, multiplet);

2.93 - 3.04 (1H, multiplet);

3.25 & 3.26 (together 6H, two singlets);

3.31 - 3.60 (5H, multiplet);

3.77 (1H, doublet of doublets, $J = 12.23$ & 6.63 Hz);

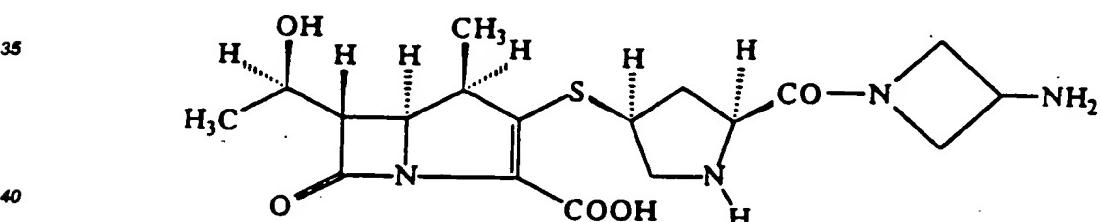
4.00 - 4.10 (3H, multiplet);

4.21 - 4.29 (2H, multiplet);

4.42 - 4.86 (6H, multiplet).

EXAMPLE 49

30 (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-(3-Aminoazetidin-1-ylcarbonyl)-pyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid



40 3630 mg of 4-nitrobenzyl (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-(3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate [prepared as described in Example 33(1)] were dissolved in 190 ml of a 3 : 2 by volume mixture of tetrahydrofuran and water, and 5500 mg of a 10% w/w palladium-on-carbon catalyst were added to the resulting solution. The mixture was then hydrogenated at 30°C for 1.5 hours in an atmosphere of hydrogen. At the end of this time, the catalyst was removed by filtration. the filtrate was washed with diethyl ether and the resulting aqueous solution was concentrated to 10 ml by evaporation under reduced pressure. The resulting solution was subjected to reverse phase silica gel column chromatography (Cosmosil 75C₁₈-prep, 250 ml, manufactured by Nacalai Tesque), eluted with mixtures of acetonitrile and water in proportions of 0 : 100, 2 : 98, 4 : 96, 6 : 94 by volume, in that order. The fractions containing the title compound were collected, concentrated by evaporation under reduced pressure and freeze-dried, to obtain 901 mg of the title compound as a powder.

45 Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

298.5.

50 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1755, 1642, 1594, 1464, 1387.

55 Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethyl-

silylpropionat) δ ppm:

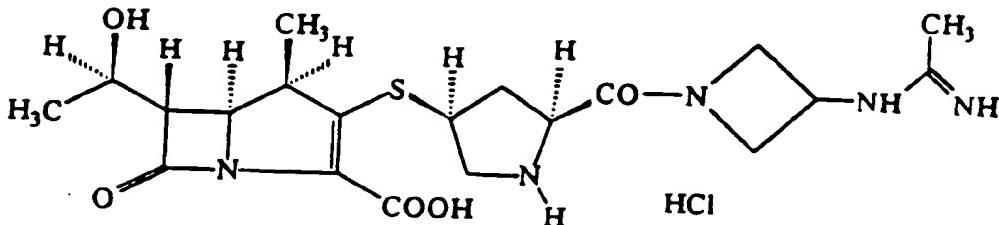
- 1.22 (3H, doublet, $J = 7.2$ Hz);
- 1.29 (3H, doublet, $J = 5.3$ Hz);
- 1.75 - 1.85 (1H, multiplet);
- 2.70 - 2.83 (1H, multiplet);
- 3.14 - 3.21 (1H, multiplet);
- 3.35 - 3.47 (3H, multiplet);
- 3.82 - 3.92 (1H, multiplet);
- 3.96 - 4.03 (1H, multiplet);
- 4.05 - 4.18 (2H, multiplet);
- 4.19 - 4.28 (3H, multiplet);
- 4.34 - 4.43 (1H, multiplet);
- 4.56 - 4.65 (1H, multiplet).

15 EXAMPLE 50

(1R,5S,6S)-2-[(2S,4S)-2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride

20

25



30

0.40 g of (1R,5S,6S)-2-[(2S,4S)-2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid (prepared as described in Example 34) was dissolved in 20 ml of cold water. 0.88 ml of 1N aqueous hydrochloric acid was added to the resulting solution, and the mixture was freeze-dried, to obtain 400 mg of the title compound as a colourless powder.

35

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

296.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1760, 1664, 1630, 1585, 1463, 1378, 1286, 1148.

40

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.01 (3H, doublet, $J = 7.17$ Hz);

1.09 (3H, doublet, $J = 6.37$ Hz);

1.76 - 1.86 (1H, multiplet);

2.07 (3H, singlet);

2.70 - 2.82 (1H, multiplet);

45

3.10 - 3.30 (3H, multiplet);

3.55 (1H, doublet of doublets, $J = 12.9$ & 6.54 Hz);

3.78 - 3.96 (2H, multiplet);

4.00 - 4.17 (3H, multiplet);

50

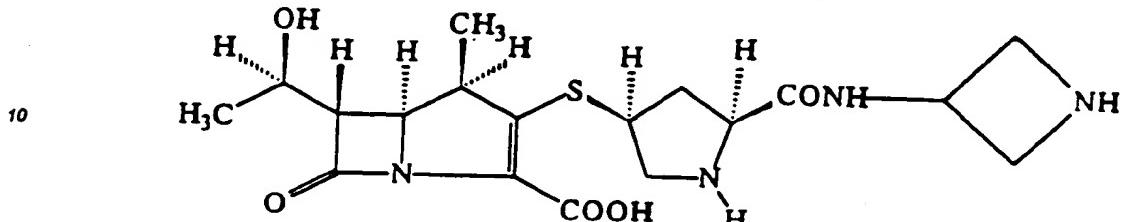
4.26 - 4.67 (4H, multiplet).

55

EXAMPLE 51

(1R,5S,6S)-2-[(2S,4S)-(Azetidin-3-ylcarbamoyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid

5



15

Following a procedure similar to that described in Example 33(1), followed by a procedure similar to that described in Example 49, but using 0.80 g of 4-nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (prepared as described in Preparation 32) and 0.95 g of (2S,4S)-4-mercapto-2-[1-(4-nitrobenzyl)oxycarbonyl]azetidin-3-ylaminocarbonyl-1-(4-nitrobenzyl)oxycarbonylpyrrolidine (prepared as described in Preparation 33), 86 mg of the title compound was obtained.

20

Ultraviolet Absorption Spectrum (H_2O), λ_{max} nm:

301.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1754, 1590, 1450, 1389, 1287, 1264.

25

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.22 (3H, doublet, $J = 7.25$ Hz);

1.30 (3H, doublet, $J = 6.36$ Hz);

1.83 - 1.93 (1H, multiplet);

30

2.72 - 2.82 (1H, multiplet);

2.88 (1H, doublet of doublets, $J = 11.64$ & 5.19 Hz);

3.34 - 3.48 (3H, multiplet);

3.65 - 3.82 (4H, multiplet);

4.04 (1H, triplet, $J = 11.67$ Hz);

35

4.19 - 4.29 (2H, multiplet);

4.34 (1H, doublet of doublets, $J = 9.02$ & 5.98 Hz);

4.40 - 4.48 (1H, multiplet).

PREPARATION 1

40

(2S,4S)-4-Mercapto-2-[4-(4-nitrobenzyl)oxycarbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyl)oxycarbonylpyrrolidine trifluoromethanesulphonate

1(a) 1-Amidino-4-t-butoxycarbonylpiperazine hemisulphate

45

2.50 g of 1-amidinopiperazine hemisulphate were dissolved in 60 ml of a 1 : 1 by volume mixture of tetrahydrofuran and water, and a solution of 3.40 g of di-t-butyl dicarbonate in 10 ml of tetrahydrofuran was added to the resulting solution, after which the mixture was stirred at room temperature for 2.5 hours. At the end of this time, the tetrahydrofuran was removed from the reaction mixture by distillation under reduced pressure, the insolubles were filtered off and the filtrate was evaporated to dryness under reduced pressure. The resulting residue was extracted with ethanol (twice, each time with 50 ml) and methanol (twice, each time with 50 ml). The extract was evaporated to dryness to obtain 2.48 g of the title compound, as crystals, melting at 278°C (with decomposition).

50

Nuclear Magnetic Resonance Spectrum (270MHz, D_2O , internal standard substance: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

1.47 (9H, singlet);

3.49 - 3.64 (8H, multiplet).

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1696, 1656, 1616, 1416, 1169, 1121.

1(b) 4-t-Butoxycarbonyl-1-(4-nitrobenzyl oxy carbonylamidin) piperazin

5 2.22 g of 1-amidino-4-t-butoxycarbonylpiperazine hemisulphate [prepared as described in step (a) above] were dissolved in 90 ml of a 1 : 1 by volume mixture of tetrahydrofuran and water, and a solution of 1.89 g of 4-nitrobenzyloxycarbonyl chloride in 16 ml of tetrahydrofuran and 16 ml of a 1N aqueous solution of sodium hydroxide were added thereto at the same time, whilst stirring and ice-cooling. The resulting mixture was stirred for 30 minutes under the same conditions, and then the organic solvent was removed from the reaction mixture
 10 by distillation under reduced pressure. The residual aqueous solution was extracted with ethyl acetate, and the ethyl acetate extract was washed with an aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. The mixture was then concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, eluted with a 4 : 1 by volume mixture of ethyl acetate and hexane. The fraction containing the desired compound was concentrated by evaporation under reduced pressure, to obtain 2.32 g of the title compound, as an amorphous powder.
 15 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

1.47 (9H, singlet);
 3.45 - 3.61 (8H, multiplet);
 5.21 (2H, singlet);
 20 6.90 - 7.20 (2H, broad);
 7.56 (2H, doublet, J = 8.6 Hz);
 8.20 (2H, doublet, J = 8.6 Hz).

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1698, 1652, 1601, 1547, 1523, 1279.

25 1(c) 1-(4-Nitrobenzyloxycarbonylamidino)piperazine

750 mg of 4-t-butoxycarbonyl-1-(4-nitrobenzyloxycarbonylamidino)piperazine [prepared as described in step (b) above] were dissolved in 10 ml of trifluoroacetic acid, and the resulting solution was stirred at room temperature for 30 minutes. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the resulting residue was dissolved in a mixture of ethyl acetate and water, and an aqueous solution of sodium hydrogencarbonate was added thereto to make the mixture alkaline. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate three times. The ethyl acetate layer and all of the ethyl acetate washings were combined and concentrated by evaporation under reduced pressure, to obtain 530 mg of the title compound, as a powder.

Nuclear Magnetic Resonance Spectrum (270MHz, D₂O, internal standard: tetradeuterated sodium trimethylsilylpropionate) δ ppm:

3.27 (4H, triplet, J = 5.3 Hz);
 3.80 (4H, triplet, J = 5.3 Hz);
 40 5.25 (2H, singlet);
 7.61 (2H, doublet, J = 8.6 Hz);
 8.27 (2H, doublet, J = 8.6Hz).

45 1(d) (2S,4S)-4-(4-Methoxybenzylthio)-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

740 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxy)pyrrolidine-2-carboxylic acid was dissolved in 7.4 ml of dry acetonitrile, and 330 mg of N,N'-carbonyldiimidazole were added to the resulting solution, after which the mixture was stirred at room temperature for 30 minutes. At the end of this time, a solution of 525 mg of 1-(4-nitrobenzyloxycarbonylamidino)piperazine [prepared as described in step (c) above] dissolved in 10 ml of acetonitrile was added to the resulting mixture, and the mixture was left to stand overnight under the same conditions. The reaction mixture was then diluted with ethyl acetate, after which it was washed with an aqueous solution of sodium hydrogencarbonate, with water and with an aqueous solution of sodium chloride, in that order, dried over anhydrous sodium sulphate and concentrated by evaporation under reduced pressure.
 55 The resulting residue was subjected to silica gel column chromatography, eluted first with ethyl acetate alone and then with a 4 : 1 by volume mixture of ethyl acetate and acetonitrile, in that order. The fractions containing the desired compound were concentrated by evaporation under reduced pressure, to obtain 890 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1709, 1652, 1608, 1520, 1439, 1346.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

- 5 1.72 - 1.89 (1H, multiplet);
- 2.39 - 2.52 (1H, multiplet);
- 3.03 - 3.18 (1H, multiplet);
- 3.30 - 4.10 (15H, multiplet);
- 4.51 - 4.62 (1H, multiplet);
- 4.98 - 5.32 (4H, multiplet);
- 10 6.85 (2H, doublet, J = 8.8 Hz);
- 7.23 (2H, doublet, J = 8.8 Hz);
- 7.40 - 7.58 (4H, multiplet);
- 8.15 - 8.25 (4H, multiplet).

15 1(e) (2S,4S)-4-Mercapto-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine trifluoromethanesulphonate

880 mg of (2S,4S)-4-(4-methoxybenzylthio)-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (d) above] were dissolved in a mixture of 4.4 ml of trifluoroacetic acid and 0.88 ml of anisole, and then 160 μl of trifluoromethanesulphonic acid were added dropwise to this solution, whilst stirring and ice-cooling. The resulting mixture was then stirred at room temperature for 3 hours, after which it was concentrated by evaporation under reduced pressure. The resulting residue was washed three times with diethyl ether, and the powder thus formed was dried to obtain 918 mg of the title compound, as a powder.

25 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1761, 1671, 1618, 1523, 1443, 1348, 1285, 1246, 1225, 1169.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

- 30 1.60 - 1.76 (1H, multiplet);
- 2.65 - 2.82 (1H, multiplet);
- 3.05 - 3.80 (10H, multiplet);
- 3.94 & 4.05 (together 1H, two doublets of doublets, J = 9.8 and 6.8 Hz);
- 4.74 & 4.83 (together 1H, two triplets, J = 7.8 Hz);
- 5.05 - 5.25 (2H, multiplet);
- 5.40 (2H, singlet);
- 35 7.53 & 7.63 (together 2H, two doublets, J = 8.8 Hz);
- 7.72 (2H, doublet, J = 8.8 Hz);
- 8.21 & 8.23 (together 2H, two doublets, J = 8.8 Hz);
- 8.28 (2H, doublet, J = 8.8 Hz).

40 PREPARATION 2

(2S,4S)-4-Mercapto-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine

45 2(a) 1-(4-Nitrobenzyloxycarbonylamidino)piperazine bis(trifluoroacetate)

750 mg of 4-t-butoxycarbonyl-1-(4-nitrobenzyloxycarbonylamidino)piperazine [prepared as described in Preparation 1(b)] were dissolved in 12 ml of trifluoroacetic acid, and the resulting solution was stirred at room temperature for 30 minutes. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and diethyl ether was added to the residue. The powder thus formed was washed three times with diethyl ether and then dried to obtain 1010 mg of the title compound, as a colourless powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1771, 1698, 1665, 1623, 1518, 1353, 1221, 1197.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

- 55 3.21 (4H, triplet, J = 5.4 Hz);
- 3.73 (4H, triplet, J = 5.4 Hz);
- 5.31 (2H, singlet);
- 7.68 (2H, doublet, J = 8.8 Hz);
- 8.26 (2H, doublet, J = 8.8 Hz).

2(b) (2S,4S)-4-(4-Methoxybenzylthio)-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine

480 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-methylpyrrolidine-2-carboxylic acid were suspended in 20 ml of dry acetonitrile, and 325 mg of N,N'-carbonyldiimidazole were added to this suspension, after which the mixture was stirred at 40°C for 1 hour. At the end of this time, the reaction mixture was cooled with ice, and 980 mg of 1-(4-nitrobenzyloxycarbonylamidino)piperazine bis(trifluoroacetate) [prepared as described in step (a) above] and 320 µl of diisopropylethylamine were added to the mixture, which was then stirred at room temperature overnight. At the end of this time, the reaction mixture was diluted with ethyl acetate and washed with an aqueous solution of sodium hydrogencarbonate, with water (4 times) and with an aqueous solution of sodium chloride, in that order. The ethyl acetate solution was dried over anhydrous sodium sulphate and then concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, eluted with a 4 : 1 by volume mixture of ethyl acetate and methanol. The fraction containing the desired compound was concentrated by evaporation under reduced pressure, to obtain 860 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1648, 1609, 1542, 1513, 1440, 1346, 1303, 1273, 1239.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

- 1.78 (1H, doubled doublet of doublets, J = 13.7, 9.3 & 5.4 Hz);
- 2.33 (3H, singlet);
- 2.48 - 2.60 (2H, multiplet);
- 3.03 - 3.24 (3H, multiplet);
- 3.70 (2H, singlet);
- 3.80 (3H, singlet);
- 3.45 - 4.15 (8H, multiplet);
- 5.21 (2H, singlet);
- 6.84 (2H, doublet, J = 8.8 Hz);
- 7.20 (2H, doublet, J = 8.8 Hz);
- 7.56 (2H, doublet, J = 8.8 Hz);
- 8.20 (2H, doublet, J = 8.8 Hz).

2(c) (2S,4S)-4-Mercapto-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine

1450 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine [prepared as described in step (b) above] were dissolved in a mixture of 7.25 ml of trifluoroacetic acid and 1.45 ml of anisole, and then 562 µl of trifluoromethanesulphonic acid were added dropwise, whilst stirring and ice-cooling, to the resulting solution. The reaction mixture was stirred for 60 minutes under the same conditions and then at room temperature for 30 minutes, after which it was concentrated by evaporation under reduced pressure. The resulting residue was washed three times with diethyl ether, and the powder thus formed was dried to obtain 1940 mg of the bis(trifluoromethanesulphonate) of the title compound as a powder.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulphoxide + D₂O, 270 MHz) δ ppm:

- 1.81 (1H, doubled doublet of doublets, J = 13.2, 9.3 & 8.8 Hz);
- 2.82 (3H, singlet);
- 2.98 (1H, doublet of triplets, J = 13.2 & 7.8 Hz);
- 3.28 - 3.81 (11H, multiplet);
- 4.63 (1H, triplet, J = 8.8 Hz);
- 5.40 (2H, singlet);
- 7.72 (2H, doublet, J = 8.8 Hz);
- 8.28 (2H, doublet, J = 8.8 Hz).

The whole of this salt was dissolved in aqueous ethyl acetate, and an aqueous solution of sodium hydrogencarbonate was added to the resulting solution to make it alkaline. The ethyl acetate layer was separated, washed with an aqueous solution of sodium chloride, dried over anhydrous sodium sulphate and concentrated by evaporation under reduced pressure, to obtain 1.21 g of the title compound, in the form of an amorphous powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1648, 1605, 1544, 1520, 1440, 1346, 1304, 1273, 1232.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

1.91 (1H, doubled doublet f doublets, J = 13.7, 8.3 & 4.9 Hz);
 2.36 (3H, singlet);
 2.65 - 2.80 (2H, multiplet);
 3.08 (1H, doublet f doublets, J = 10.2 & 2.9 Hz);
 5 3.24 (1H, triplet, J = 8.3 Hz);
 3.32 - 3.44 (1H, multiplet);
 3.46 - 4.00 (8H, multiplet);
 5.21 (2H, singlet);
 7.56 (2H, doublet, J = 8.8 Hz);
 10 8.19 (2H, doublet, J = 8.8 Hz).

PREPARATIONS 3 TO 21

15 The Compounds of Preparations 3 to 21 were synthesized in the same manner as described in Prepara-tions 1 and 2.

Preparation 3

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[4-(4-nitrobenzyloxycarbonylamidino)homopiperazin-1-yl-carbonyl] pyrrolidine
 20 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:
 1708, 1651, 1605, 1551, 1520, 1441, 1346, 1284.
 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:
 25 1.75 - 1.98 (3H, multiplet);
 2.00 - 2.20 (1H, multiplet);
 2.66 - 2.82 (1H, multiplet);
 3.13 - 3.96 (8H, multiplet);
 4.06 - 4.15 (2H, multiplet);
 4.61 (1H, triplet, J = 8.0 Hz);
 30 5.10 - 5.25 (4H, multiplet);
 7.42 - 7.58 (4H, multiplet);
 8.16 - 8.23 (4H, multiplet).

Preparation 4

35 (2S,4S)-4-Mercapto-1-methyl-2-[4-(4-nitrobenzyloxycarbonylamidino)homopiperazin-1-ylcarbonyl]pyrrolidine
 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:
 1641, 1607, 1552, 1520, 1486, 1444, 1347, 1285.
 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:
 40 1.81 - 2.01 (3H, multiplet);
 2.63 - 2.75 (1H, multiplet);
 2.80 - 2.88 (1H, multiplet);
 3.07 - 3.15 (1H, multiplet);
 3.23 - 3.93 (10H, multiplet);
 45 5.21 (2H, singlet);
 7.54 - 7.57 (2H, multiplet);
 8.17 - 8.22 (2H, multiplet).

Preparation 5

50 (2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[4-(4-nitrobenzyloxycarbonylguanidino)piperidin-1-ylcarbo-nyl]pyrrolidine

Preparation 6

55 (2S,4S)-4-Mercapto-1-methyl-2-[4-(4-nitrobenzyloxycarbonylguanidino)piperidin-1-ylcarbonyl]pyrrolidine

Preparation 7

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-3-(4-nitrobenzyloxycarbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine

5

Preparation 8

(2S,4S)-4-Mercapto-1-methyl-2-[(3S)-3-(4-nitrobenzyloxycarbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine

10 Preparation 9

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[3-(4-nitrobenzyloxycarbonylguanidino)azetidin-1-ylcarbonyl]pyrrolidine

15 Preparation 10

(2S,4S)-4-Mercapto-1-methyl-2-[3-(4-nitrobenzyloxycarbonylguanidino)azetidin-1-ylcarbonyl]pyrrolidine

20 Preparation 11

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylguanidino)ethylcarbamoyl]pyrrolidine

25 Preparation 12

(2S,4S)-4-Mercapto-1-methyl-2-[2-(4-nitrobenzyloxycarbonylguanidino)ethylcarbamoyl]pyrrolidine

30 Preparation 13

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[4-(methyl-4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine

35 Preparation 14

(2S,4S)-4-Mercapto-1-methyl-2-[4-(methyl-4-nitrobenzyloxycarbonylamidino)piperazin-1-ylcarbonyl]pyrrolidine

40 Preparation 15

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(3R)-3-(4-nitrobenzyloxycarbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine

45 Preparation 16

(2S,4S)-4-Mercapto-1-methyl-2-[(3R)-3-(4-nitrobenzyloxycarbonylguanidino)pyrrolidin-1-ylcarbonyl]pyrrolidine

50 Preparation 17

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-4-(4-nitrobenzyloxycarbonylamidino)3-methylpiperazin-1-ylcarbonyl]pyrrolidine

55 Preparation 18

(2S,4S)-4-Mercapto-1-methyl-2-[(3R)-4-(4-nitrobenzyloxycarbonylamidino)-3-methylpiperazin-1-ylcarbonyl]pyrrolidine

Preparation 19

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[1-(4-nitrobenzyloxycarbonylamidino)piperidin-4-ylcarbamoyl]pyrrolidine

5

Preparation 20

(2S,4S)-4-Mercapto-1-[1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-1-(4-nitrobenzyloxycarbonylamidino)pyrrolidin-3-ylcarbamoyl]pyrrolidine

10

Preparation 21

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[1-(4-nitrobenzyloxycarbonylamidino)azetidin-3-ylcarbamoyl]pyrrolidine

15

PREPARATION 22

(2S,4S)-4-Mercapto-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

20

22(a) (2S,4S)-2-(3-Aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

2.05 g of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidine carboxylic acid were dissolved in 20 ml of dry acetonitrile, and 0.78 g of N,N'-carbonyldiimidazole was added to the resulting solution, after which the mixture was stirred at 40°C for 1 hour. The resulting mixture was then added dropwise to a solution of 1.00 g of 3-aminoazetidine dihydrochloride and 2.40 ml of diisopropylethylamine in 10 ml of methanol, whilst ice-cooling, and the mixture was stirred at the same temperature for 1 hour. At the end of this time, the reaction mixture was filtered, and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was subjected to silica gel column chromatography (silica gel 60 9385, manufactured by Merck, 100 g) to give 2.56 g of the title compound, in the form of an amorphous powder, from the fraction obtained by elution with a 65 : 35 by volume mixture of ethyl acetate and methanol.

25 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:
1708, 1660, 1609, 1513, 1442, 1404, 1346, 1248.

20 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:
1.88 - 2.04 (1H, multiplet);

2.38 - 3.20 (4H, multiplet);
3.25 - 3.34 (1H, multiplet);

3.67 - 4.62 (6H, multiplet);
3.72 (2H, singlet);

3.78 & 3.79 (together 3H, two singlets);
5.09 - 5.37 (2H, multiplet);

6.84 (2H, doublet, J = 8.78 Hz);
7.22 (2H, doublet, J = 8.78 Hz);

7.45 (2H, doublet, J = 8.78 Hz);
8.21 (2H, doublet, J = 8.78 Hz).

25 50 22(b) (2S,4S)-4-(4-Methoxybenzylthio)-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

0.81 g of (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (a) above] was dissolved in 20 ml of methylene chloride, and 0.32 g of diisopropylethylamine and 0.40 g of p-nitrobenzyl chloroformate were added to the resulting solution, whilst ice-cooling. The resulting mixture was then stirred at the same temperature for 40 minutes. At the end of this time, the reaction mixture was diluted with ethyl acetate and washed with water and with an aqueous

solution of sodium chloride, in that order. The ethyl acetate layer was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The residue was subjected to silica gel column chromatography (silica gel 60 9385, manufactured by Merck, 40 g) to give 0.64 g of the title compound, in the form of an amorphous powder, from the fraction obtained by elution with a 99 : 1 by volume mixture of ethyl acetate and methanol.

5 Infrared Absorption Spectrum (CHCl_3), ν_{max} cm⁻¹:

1725, 1662, 1608, 1521, 1440, 1347, 1250.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl_3) δ ppm:

10 1.94 - 2.04 (1H, multiplet);

2.31 - 2.48 (1H, multiplet);

3.04 - 3.12 (1H, multiplet);

3.26 - 3.34 (1H, multiplet);

3.72 (2H, singlet);

3.79 (3H, singlet);

15 3.81 - 3.99 (1H, multiplet);

4.08 - 4.87 (6H, multiplet);

5.09 - 5.72 (5H, multiplet);

6.82 - 6.87 (2H, multiplet);

7.23 (2H, doublet, $J = 8.30$ Hz);

20 7.45 & 7.50 (together 4H, two doublets, $J = 8.79$ Hz);

8.22 & 8.23 (together 4H, two doublets, $J = 8.79$ Hz).

22(c) (2S,4S)-4-Mercapto-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

25

0.59 g of (2S,4S)-4-(4-methoxybenzylthio)-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (b) above] was suspended in 0.94 ml of anisole, and 3.32 ml of trifluoroacetic acid and 0.15 ml of trifluoromethanesulphonic acid were added drop-wise to the suspension, whilst ice-cooling, after which the mixture was stirred at the same temperature for 1 hour. At the end of this time, 1,2-dichloroethane was added to the reaction mixture, and the solvent was removed by distillation under reduced pressure. The residue was then washed by repeated decantation, in turn, with hexane and with diethyl ether. The residue was diluted with ethyl acetate and made alkaline by the addition of an aqueous solution of sodium hydrogencarbonate. The ethyl acetate layer was separated and washed with water and with an aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure to give 0.44 g of the title compound, in the form of an amorphous powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1709, 1656, 1521, 1440, 1405, 1347, 1257.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide, 270 MHz) δ ppm:

40 1.62 - 1.85 (1H, multiplet);

2.58 - 2.69 (1H, multiplet);

3.05 - 3.25 (2H, multiplet);

3.70 - 4.55 (8H, multiplet);

5.08 - 5.28 (4H, multiplet);

45 7.55 - 7.65 (4H, multiplet);

8.11 - 8.25 (5H, multiplet).

PREPARATION 23

50

(2S,4S)-4-Mercapto-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

23(a) (2S,4S)-4-(4-Methoxybenzylthio)-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

55

0.78 g of (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in Preparation 22(a)] was dissolved in 15 ml of ethyl acetate, and 0.78 ml of a 4N solution of hydrogen chloride in ethyl acetate was added to the resulting solution, whilst ice-cooling.

Diethyl ether was added to the reaction mixture, and the resulting powder was filtered off and dried, to give 0.79 g of (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine hydrochloride.

0.78 g of this compound was suspended in 20 ml of dry acetonitrile, and 0.51 g of N-(4-nitrobenzyl oxy carbonyl)acetamidine was added to the suspension, after which the mixture was stirred at 50°C for 80 minutes. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was diluted with ethyl acetate, washed with water and with an aqueous solution of sodium chloride, in that order, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography (silica gel 60 9385, manufactured by Merck, 150 ml) to give 0.99 g of the title compound, in the form of an amorphous powder, from the fraction obtained by elution with a 95 : 5 by volume mixture of ethyl acetate and methanol.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1707, 1667, 1608, 1551, 1520, 1442, 1346, 1238.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

15 1.29 - 2.59 (7H, multiplet);
 3.05 - 3.14 (1H, multiplet);
 3.26 - 3.34 (1H, multiplet);
 3.67 - 4.86 (6H, multiplet);
 3.73 (2H, singlet);
 20 3.79 (3H, singlet);
 5.09 - 5.33 (4H, multiplet);
 6.85 (2H, doublet, J = 8.79 Hz);
 7.23 (2H, doublet, J = 8.79 Hz);
 7.44 - 7.65 (4H, multiplet);
 25 8.19 - 8.25 (4H, multiplet).

23(b) (2S,4S)-4-Mercapto-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

30 0.99 g of (2S,4S)-4-(4-methoxybenzylthio)-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-yl-carbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (a) above] was dissolved in 1.49 ml of anisole, and 10 ml of trifluoroacetic acid and 0.24 ml of trifluoromethanesulphonic acid were added dropwise to the resulting solution. The resulting mixture was stirred at the same temperature for 40 minutes and then at room temperature for 50 minutes, after which 1,2-dichloroethane was added to the reaction mixture. The mixture was then concentrated by evaporation under reduced pressure. The resulting residue was washed by repeated decantation, in turn, with hexane and diethyl ether, and the mixture was then diluted with ethyl acetate, and made alkaline by the addition of an aqueous solution of sodium hydrogencarbonate. The ethyl acetate layer was washed with water and with an aqueous solution of sodium chloride, in that order, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure, to give 0.82 g of the title compound, in the form of an amorphous powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1708, 1664, 1607, 1551, 1521, 1442, 1346, 1228.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

45 1.73 - 2.65 (4H, multiplet);
 2.23 (3H, singlet);
 3.23 - 3.54 (2H, multiplet);
 3.78 - 4.94 (7H, multiplet);
 5.11 - 5.37 (4H, multiplet);
 7.48 - 7.59 (4H, multiplet);
 50 8.22 & 8.23 (together 4H, two doublets, J = 8.79 Hz).

PREPARATION 24

(2S,4S)-4-Mercapto-2-[3-(N-4-nitrobenzyloxycarbonylformimidoylamino)azetidin-1-ylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

Following a procedure similar to that described in Preparation 23, but using (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine hydrochloride and N-(4-nitro-

benzyloxycarbonyl)formamidine as starting materials, in relative proportions similar to those used in that Preparation, the title compound was obtained.

PREPARATION 25

5

(2S,4S)-4-Mercapto-1-methyl-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]pyrrolidine

25(1) (2S,4S)-2-(3-Aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-methylpyrrolidine

10 1.62 g of (2S,4S)-4-(4-methoxybenzylthio)-1-methyl-2-pyrrolidinecarboxylic acid were suspended in 20 ml of dry acetonitrile, and 1.02 g of N,N'-carbonyldiimidazole were added to the suspension, after which the mixture was stirred at 40°C for 45 minutes. A solution of 1.00 g of 3-aminoazetidine dihydrochloride and 2.40 ml of diisopropylethylamine in 10 ml of methanol was added dropwise to the mixture, whilst ice-cooling, and the mixture was stirred at the same temperature for 90 minutes. At the end of this time, the reaction mixture
15 was concentrated by evaporation under reduced pressure. The resulting residue was subjected to reverse phase column chromatography (Cosmosil 75C₁₈-PREP, manufactured by Nacalai Tesque, 145 g) to give 1.21 g of the title compound, as a colourless oil, from the fraction obtained by elution with 30% by volume aqueous acetonitrile.

Infrared Absorption Spectrum (CHCl₃), ν_{max} cm⁻¹:
20 1618, 1510, 1465, 1246, 1176.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

25 1.77 - 2.00 (3H, multiplet);
2.30 (3H, singlet);
2.45 - 2.56 (2H, multiplet);
2.88 - 2.95 (1H, multiplet);
3.00 - 3.16 (2H, multiplet);
3.70 (2H, multiplet - central value reported);
3.80 (3H, multiplet - central value reported);
3.65 - 4.06 (3H, multiplet);
30 4.23 - 4.33 (1H, multiplet);
4.50 - 4.68 (1H, multiplet);
6.81 - 6.87 (2H, multiplet);
7.18 - 7.24 (2H, multiplet).

35 25(b) (2S,4S)-4-(4-Methoxybenzylthio)-1-methyl-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]pyrrolidine

40 0.60 g of (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-methylpyrrolidine [prepared as described in step (a) above] was dissolved in 18 ml of methylene chloride, and 0.38 ml of diisopropylethylamine and 0.46 g of p-nitrobenzyl chloroformate were added to the resulting solution, whilst ice-cooling, after which the mixture was stirred at the same temperature for 30 minutes. At the end of this time, the reaction mixture was diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography (silica gel 60 9385, manufactured by Merck, 40 g), to give 0.85 g of the title compound, in the form of an amorphous powder, from the fraction obtained by elution with a 95 : 5 by volume mixture of ethyl acetate and methanol.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1725, 1637, 1610, 1512, 1463, 1346, 1251.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

50 1.77 - 1.95 (1H, multiplet);
2.32 & 2.36 (together 3H, two singlets);
2.49 - 2.66 (2H, multiplet);
2.98 - 3.14 (3H, multiplet);
3.69 (2H, singlet);
55 3.80 (3H, singlet);
3.73 - 3.94 (1H, multiplet);
4.11 - 4.83 (4H, multiplet);
5.20 (2H, multiplet - central value reported);

- 5.40 - 5.51 (1H, multiplet);
 6.81 - 6.87 (2H, multiplet);
 7.18 - 7.22 (2H, multiplet);
 7.51 (2H, doublet, J = 8.79 Hz);
 8.22 (2H, doublet, J = 8.79 Hz).

25(c) (2S,4S)-4-Mercapto-1-methyl-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]pyrrolidine

10 0.73 g of (2S,4S)-4-(4-methoxybenzylthio)-1-methyl-2-[3-(4-nitrobenzyloxycarbonylamino)azetidin-1-ylcarbonyl]pyrrolidine [prepared as described in step (b) above] was dissolved in 1.53 ml of anisole, and 7.25 ml of trifluoroacetic acid and 0.25 ml of trifluoromethanesulphonic acid were added dropwise, whilst ice-cooling, to the resulting solution. The mixture was then stirred at room temperature for 90 minutes, after which 1,2-dichloroethane was added to the reaction mixture and the solvent was removed by evaporation under reduced pressure. The resulting residue was washed by repeated decantation, in turn, with hexane and with diethyl ether. The residue was diluted with ethyl acetate and was made alkaline by the addition of an aqueous solution of sodium hydrogen carbonate. The ethyl acetate layer was washed with water and with an aqueous solution of sodium chloride, in that order, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure, to give 420 mg of the title compound, in the form of an amorphous powder.

15 Infrared Absorption Spectrum (liquid film), ν_{max} cm⁻¹:

20 1721, 1638, 1609, 1522, 1460, 1347, 1258.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 25 1.85 - 2.12 (2H, multiplet);
 2.35 & 2.37 (together 3H, two singlets);
 2.63 - 2.82 (2H, multiplet);
 3.00 - 3.10 (2H, multiplet);
 3.30 (1H, broad singlet);
 3.86 - 3.96 (1H, multiplet);
 4.08 - 4.79 (4H, multiplet);
 5.21 (2H, singlet);
 30 5.40 - 5.62 (1H, multiplet);
 7.51 (2H, doublet, J = 8.79 Hz);
 8.22 (2H, doublet, J = 8.79 Hz).

PREPARATION 26

35

(2S,4S)-4-Mercapto-1-methyl-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbonyl]pyrrolidine

40

26(a) (2S,4S)-4-(4-Methoxybenzylthio)-1-methyl-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbonyl]pyrrolidine

45 540 mg of (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-methylpyrrolidine [prepared as described in Preparation 25(a)] were dissolved in 15 ml of ethyl acetate and 5 ml of methylene chloride, and 1.61 ml of a 4N solution of hydrogen chloride in ethyl acetate were added to the resulting solution, whilst ice-cooling. The mixture was then stirred at the same temperature for 30 minutes, after which it was diluted with diethyl ether, and a powder was filtered off and dried to give 650 mg of a hydrochloride.

50 650 mg of this hydrochloride, 415 mg of N-(4-nitrobenzyloxycarbonyl)acetamide and 277 μl of diisopropylethylamine were suspended in 10 ml of dry acetonitrile, after which the mixture was stirred at 55°C for 1 hour. At the end of this time, insolubles were filtered from the reaction mixture and the filtrate was concentrated by evaporation under reduced pressure. The residue was subjected to silica gel column chromatography to give 622 mg of the title compound, as a powder, from the fraction obtained by elution with a 45 : 45 : 5 by volume mixture of methylene chloride, ethyl acetate and methanol.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

55 1682, 1638, 1609, 1553, 1512, 1454, 1348, 1225, 1190, 1080.

55 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

- 1.60 - 2.38 (7H, multiplet);
 2.43 - 2.68 (2H, multiplet);
 2.83 - 3.20 (3H, multiplet);

3.69 (2H, singlet);
 3.79 (3H, singlet);
 3.84 - 5.02 (5H, multiplet);
 5 5.22 (2H, singlet);
 6.84 (2H, doublet, J = 8.79 Hz);
 7.20 (2H, doublet, J = 8.79 Hz);
 7.51 - 7.62 (2H, multiplet);
 8.15 - 8.28 (2H, multiplet).

10 26(b) (2S,4S)-4-Mercapto-1-methyl-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbo-nyl]pyrrolidine

15 610 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-methyl-2-[3-(N-4-nitrobenzyloxycarbonylacetimidoylamino)azetidin-1-ylcarbonyl]pyrrolidine [prepared as described in step (a) above] were dissolved in 1.19 ml of anisole, and 4.23 ml of trifluoroacetic acid and 193 µl of trifluoromethanesulphonic acid were added to the resulting solution, whilst ice-cooling. The mixture was then stirred for 1 hour under the same conditions and then at room temperature for a further 1 hour. At the end of this time, the solvent was removed by distillation under reduced pressure, and the resulting residue was washed with hexane and with diethyl ether and dried by evaporation under reduced pressure, to convert it to the trifluoromethanesulphonate in the form of a powder. Ethyl acetate was added to the whole of this compound, followed by sufficient of a saturated aqueous solution of sodium hydrogencarbonate to make it alkaline. The ethyl acetate layer was separated, washed with an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate, and the solvent was removed by evaporation under reduced pressure, to give 448 mg of the title compound as a powder.

20 Infrared Absorption Spectrum (liquid film), ν_{max} cm⁻¹:
 1642, 1608, 1554, 1522, 1465, 1347, 1237, 1193.

25 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

1.81 - 1.98 (1H, multiplet);
 2.07 - 3.50 (11H, multiplet);
 3.83 - 5.02 (5H, multiplet);
 30 5.22 & 5.28 (together 2H, two singlets);
 7.50 - 7.62 (2H, multiplet);
 8.15 - 8.28 (2H, multiplet).

PREPARATION 27

35 (2S,4S)-4-Mercapto-1-methyl-2-[3-(N-4-nitrobenzyloxycarbonylformimidoylamino)azetidin-1-ylcarbonyl]pyrrolidine

40 A procedure similar to that described in Preparation 26 was repeated, but using (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-methylpyrrolidine hydrochloride and N-(4-nitrobenzyloxycarbonyl)-formamidine as starting materials, in relative proportions similar to those used in that Preparation, to give the title compound.

PREPARATION 28

45 (2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-3-(1-1,2,4-triazolyl)-1-pyrrolidinylcarbonyl]pyrrolidine

50 28(1) (2S,4S)-4-(4-methoxybenzylthio)-2-[(3S)-3-(1-1,2,4-triazolyl)-1-pyrrolidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

55 768 mg of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 8 ml of dry tetrahydrofuran, and the resulting solution was cooled to 0°C. 191 mg of triethylamine were added to the solution, followed by 218 mg of pivaloyl chloride, and then the mixture was stirred at the same temperature for 5 minutes. At the end of this time, a mixture of 238 mg of (3S)-3-(1-1,2,4-triazolyl)pyrrolidine trifluoroacetate, 440 mg of diisopropyl thylamine and 7 ml of dry acetonitrile was added to the mixture, and the mixture was gradually heated and then stirred at 0°C for 15 minutes and at room temperature for 2 hours. The solvent was then removed by evaporation under reduced pressure, and the residue was diluted

with ethyl acetate, after which the diluted solution was washed with an aqueous solution of sodium hydrogen-carbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography, using a 7:1 by volume mixture of ethyl acetate and methanol as the eluent, to give 803 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1709, 1656, 1512, 1346, 857, 738.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide) δ ppm:

- 1.40 - 1.70 (1H, multiplet);
- 10 2.20 - 2.80 (2H, multiplet);
- 2.95 - 3.15 (1H, multiplet);
- 3.15 - 3.95 (11H, multiplet);
- 4.35 - 4.65 (1H, multiplet);
- 5.00 - 5.30 (4H, multiplet);
- 15 6.80 - 6.95 (2H, multiplet);
- 7.20 - 7.35 (2H, multiplet);
- 7.40 - 7.70 (2H, multiplet);
- 8.00 (1H, multiplet - central value reported);
- 8.13 - 8.26 (2H, multiplet);
- 20 8.49 - 8.61 (1H, multiplet).

28(b) (2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(3S)-3-(1-1,2,4-triazolyl)-1-pyrrolidinylcarbonyl]pyrrolidine

25 783 mg of (2S,4S)-4-(4-methoxybenzylthio)-2-[(3S)-3-(1-1,2,4-triazolyl)-1-pyrrolidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (a) above] were suspended in 1.5 ml of anisole, and 7.5 ml of trifluoroacetic acid and 0.24 ml of trifluoromethanesulphonic acid were added to the resulting suspension, whilst ice-cooling, after which the mixture was stirred at room temperature for 1.5 hours. A cycle consisting of removing the solvent by evaporation under reduced pressure, washing the residue with hexane to remove anisole, adding diethyl ether to the mixture to solidify the product and milling the product, after which the mixture was decanted was repeated several times to obtain a powder. The whole of this powder was mixed with 40 ml of ethyl acetate and with an aqueous solution of sodium hydrogencarbonate, and then the organic layer was separated. The organic layer was dried over anhydrous magnesium sulphate, filtered and concentrated by evaporation under reduced pressure, to give 713 mg of the title compound, as a powder.

30 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1706, 1652, 1522, 1346, 857, 739.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide) δ ppm:

- 1.15 - 1.25 (1H, multiplet);
- 1.50 - 1.80 (1H, multiplet);
- 40 2.20 - 2.60 (2H, multiplet);
- 2.60 - 2.90 (1H, multiplet);
- 3.10 - 4.10 (8H, multiplet);
- 4.40 - 4.65 (1H, multiplet);
- 5.00 - 5.30 (2H, multiplet);
- 45 7.45 - 7.70 (2H, multiplet);
- 8.00 - 8.02 (1H, multiplet);
- 8.10 - 8.30 (2H, multiplet);
- 8.50 - 8.62 (1H, multiplet).

50 PREPARATION 29

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[3-(1-1,2,4-triazolyl)-1-azetidinylcarbonyl]pyrrolidine

29(a) (2S,4S)-4-(4-Methoxybenzylthio)-2-[3-(1-1,2,4-triazolyl)-1-azetidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

55 1.13 g of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 11 ml of dry tetrahydrofuran, and the resulting solution was cooled to 0°C. 280 mg of tri-

thylamine were added to the solution, followed by 320 mg of pivaloyl chloride, and the mixture was stirred at the same temperature for 5 minutes. At the end of this time, a mixture of 1.36 g of 3-(1-1,2,4-triazolyl)azetidine hydrochloride [prepared by a procedure similar to that described in Preparation 31(a) and (b), but using 1,2,4-triazole], 956 mg of diisopropylethylamine and 6 ml of dry acetonitrile was added to the mixture, after which the mixture was stirred at 0°C for 30 minutes and at room temperature for 30 minutes. The reaction mixture was then filtered, and the solvent was removed by evaporation under reduced pressure. The resulting residue was diluted with ethyl acetate, and the diluted solution was washed with an aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography, using a 10 : 1 by volume mixture of ethyl acetate and methanol as the eluent, to give 870 mg of the title compound, as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1708, 1665, 1512, 1346, 854, 738.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide) δ ppm:

15 1.60 - 1.80 (1H, multiplet);
 2.50 - 2.70 (1H, multiplet);
 3.00 - 3.15 (1H, multiplet);
 3.15 - 3.25 (1H, multiplet);
 3.65 - 3.90 (6H, multiplet);
 20 4.05 - 4.80 (4H, multiplet);
 5.10 - 5.50 (4H, multiplet);
 6.88 (2H, doublet, J = 8.50 Hz);
 7.27 (2H, doublet, J = 8.36 Hz);
 25 7.59 - 7.62 (2H, multiplet);
 7.90 - 8.10 (1H, multiplet);
 8.21 - 8.28 (2H, multiplet);
 8.57 - 8.66 (1H, multiplet).

29(b) (2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[3-(1-1,2,4-triazolyl)-1-azetidinylcarbonyl]pyrrolidine

30 858 mg of (2S,4S)-4-(4-methoxybenzylthio)-2-[3-(1-1,2,4-triazolyl)-1-azetidinylcarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (a) above] were suspended in 1.7 ml of anisole, and 8.4 ml of trifluoroacetic acid and 0.27 ml of trifluoromethanesulphonic acid were added to the resulting suspension, whilst ice-cooling, after which the mixture was stirred at 0°C for 30 minutes and then at room temperature for 30 minutes. At the end of this time, the solvent was removed by evaporation under reduced pressure, and the residue was washed with hexane to remove anisole. The mixture was then mixed with diethyl ether to wash the mixture further. The resulting compound was mixed with 100 ml of ethyl acetate and with 30 ml of a saturated aqueous solution of sodium hydrogen carbonate, and the organic layer was separated. 40 The organic layer was then dried over anhydrous magnesium sulphate, and the residue was filtered and concentrated by evaporation under reduced pressure, to give 873 mg of the title compound, as a white powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1706, 1663, 1522, 1347, 854, 739.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide + D₂O) δ ppm:

45 1.70 - 1.85 (1H, multiplet);
 2.60 - 2.75 (1H, multiplet);
 3.05 - 3.25 (1H, multiplet);
 3.25 - 3.40 (1H, multiplet);
 3.65 - 4.90 (7H, multiplet);
 50 5.10 - 5.50 (4H, multiplet);
 7.55 - 7.70 (2H, multiplet);
 7.95 - 8.15 (1H, multiplet);
 8.20 - 8.30 (2H, multiplet);
 8.55 - 8.70 (1H, multiplet).

PREPARATION 30(2S,4S)-2-(3-Dimethylaminoazetidin-1-ylcarbonyl)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine5 **30(a) (2S,4S)-2-(3-Dimethylaminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine**

10 644 mg of formic acid and 750 mg of a 35% by volume aqueous formaldehyde solution were added to 1.75 g of (2S,4S)-2-(3-aminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in Preparation 22(a)], and the resulting mixture was stirred at 50°C for 5 hours. The mixture was then diluted with ethyl acetate, and the diluted solution was washed with an aqueous solution of sodium hydrogencarbonate, with water and with an aqueous solution of sodium chloride, in that order. It was then dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, and the resulting residue was subjected to silica gel column chromatography. 1.45 g of the title compound were obtained, as a colourless powder, from the fraction obtained by elution with a 45 : 45 : 10 by volume mixture of methylene chloride, ethyl acetate and methanol.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1710, 1664, 1609, 1513, 1442, 1403, 1345, 1248, 1172.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 20 1.86 - 2.05 (1H, multiplet);
- 2.11, 2.13 & 2.27 (together 6H, three singlets);
- 2.34 - 2.52 (1H, multiplet);
- 2.83 - 3.36 (3H, multiplet);
- 3.73 (2H, singlet);
- 25 3.79 & 3.80 (together 3H, two singlets);
- 3.68 - 4.51 (6H, multiplet);
- 5.05 - 5.36 (2H, multiplet);
- 6.85 (2H, doublet, J = 8.52 Hz);
- 7.23 (2H, doublet, J = 8.52 Hz);
- 30 7.46 & 7.50 (together 2H, two doublets, J = 8.57 Hz);
- 8.23 (2H, doublet, J = 8.57 Hz)

30(2) (2S,4S)-2-(3-Dimethylaminoazetidin-1-ylcarbonyl)-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

35 1.47 g of (2S,4S)-2-(3-dimethylaminoazetidin-1-ylcarbonyl)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (a) above] were dissolved in 3.02 ml of anisole, and 10.71 ml of trifluoroacetic acid and 0.488 ml of trifluoromethanesulphonic acid were added to the resulting solution, after which the mixture was stirred at the same temperature for 1 hour. The solvent was then removed by distillation under reduced pressure, and the residue was washed by repeated decantation, in turn, with hexane and with diethyl ether. Ethyl acetate was added to the residue and the mixture was made alkaline by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The ethyl acetate layer was separated, washed with an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The solvent was then removed by distillation under reduced pressure, to give 1.01 g of the title compound as a powder.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1710, 1645, 1607, 1517, 1459, 1432, 1403, 1343, 1169.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 1.87 - 2.05 (2H, multiplet);
- 2.11, 2.13 & 2.25 (6H, three singlets);
- 2.58 - 2.73 (1H, multiplet);
- 2.82 - 3.46 (3H, multiplet);
- 3.75 - 4.54 (6H, multiplet);
- 5.05 - 5.37 (2H, multiplet);
- 7.50 (2H, doublet, J = 8.57 Hz);
- 8.22 (2H, doublet, J = 8.57 Hz)

PREPARATION 31(2S,4S)-2-[3-(1-imidazolyl)azetidin-1-ylcarbonyl]-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidine5 31(a) 1-Benzhydryl-3-(1-imidazolyl)azetidine

A solution of 3.20 g of imidazole in 25 ml of dimethylformamide was added to 2.10 g of a suspension of sodium hydride (as a 55% w/w dispersion in mineral oil) in 25 ml of dimethylformamide, whilst ice-cooling. The mixture was then stirred at room temperature for 1 hour. A solution of 5.00 g of 1-benzhydryl-3-methanesulphonyloxyazetidine in 50 ml of dimethylformamide was then added to the mixture, after which the mixture was stirred at 70°C for 17 hours. At the end of this time, the reaction mixture was diluted with ethyl acetate and washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was then dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography to obtain 2.88 g of the title compound, as a powder, from the fraction obtained by elution with a 95 : 5 by volume mixture of ethyl acetate and methanol.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1490, 1452, 1311, 1236, 1074, 905, 755, 707.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

20 3.23 - 3.35 (2H, multiplet);

3.60 - 3.69 (2H, multiplet);

4.43 (1H, singlet);

4.67 - 4.79 (1H, multiplet);

7.08 - 7.69 (13H, multiplet).

25

31(b) 3-(1-Imidazolyl)azetidine dihydrochloride

3.20 g of 1-benzhydryl-3-(1-imidazolyl)azetidine [prepared as described in step (a) above] were dissolved in 30 ml of methanol, and 8.90 ml of a 10% w/v solution of hydrogen chloride in methanol were added to the resulting solution. 1.60 g of a 20% w/w palladium hydroxide-on-carbon catalyst were then added to the mixture, after which the mixture was hydrogenated at 50°C for 40 minutes in an atmosphere of hydrogen. The catalyst was then removed by filtration and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was washed with diethyl ether and dried under reduced pressure, to obtain 2.03 mg of the title compound, as a powder.

35 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1581, 1554, 1509, 1435, 1303, 1092, 839, 637, 623.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide) δ ppm:

4.27 - 4.35 (2H, multiplet);

4.39 - 4.46 (2H, multiplet);

40 5.40 - 5.50 (1H, multiplet);

7.48 (1H, singlet);

8.03 (1H, singlet);

8.85 (1H, singlet).

45 31(c) (2S,4S)-2-[3-(1-Imidazolyl)azetidin-1-ylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

3.80 g of (2S,4S)-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)-2-pyrrolidinecarboxylic acid were dissolved in 40 ml of dry acetonitrile. 1.65 g of N,N'-carbonyldiimidazole were added to the resulting solution, and the mixture was stirred at 40°C for 1 hour. A solution of 2.00 g of 3-(1-imidazolyl)azetidine dihydrochloride [prepared as described in step (b) above] and 2.90 g of diisopropylethylamine dissolved in a mixture of 30 ml of dry acetonitrile and 5 ml of methanol was then added at room temperature to the reaction mixture, after which the mixture was stirred at the same temperature for 1 hour. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with water and with an aqueous solution of sodium chloride, in that order. The ethyl acetate layer was separated, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel chromatography to obtain 4.00 g of the title compound, as a powder, from the fraction obtained by elution with an 85 : 15 by volume mixture

of ethyl acetate and methanol.

Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

1706, 1667, 1609, 1512, 1442, 1403, 1346, 1245.

Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 5 2.05 - 3.38 (4H, multiplet);
- 3.75 (2H, singlet);
- 3.79 (3H, singlet);
- 4.12 - 5.45 (9H, multiplet);
- 6.84 - 8.29 (11H, multiplet).

10 31(d) (2S,4S)-2-[3-(1-imidazolyl)azetidin-1-ylcarbonyl]-4-mercaptop-1-(4-nitrobenzyloxycarbonyl)pyrrolidin

4.00 g of (2S,4S)-2-[3-(1-imidazolyl)azetidin-1-ylcarbonyl]-4-(4-methoxybenzylthio)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine [prepared as described in step (c) above] were dissolved in 7.88 ml of anisole, and 27.9 ml of trifluoroacetic acid and 1.27 ml of trifluoromethanesulphonic acid were added to the resulting solution, whilst ice-cooling, after which the mixture was stirred for 1 hour under the same conditions. At the end of this time, the solvent was removed by distillation under reduced pressure, and the residue was washed with hexane and diethyl ether and dried by evaporation under reduced pressure to give the trifluoromethanesulphonate of the title compound as a powder. Ethyl acetate was added to the whole of this compound and then sufficient of a saturated aqueous solution of sodium hydrogencarbonate was added to make it alkaline. The ethyl acetate layer was separated, washed with an aqueous solution of sodium chloride and dried over anhydrous magnesium sulphate, after which the the solvent was removed by evaporation under reduced pressure, to obtain 3.10 g of the title compound as a powder.

15 Infrared Absorption Spectrum (KBr), ν_{max} cm⁻¹:

2606, 1746, 1722, 1623, 1569, 1468, 1419, 1378, 1344, 1250.

20 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃ + D₂O) δ ppm:

- 25 2.01 - 3.50 (4H, multiplet);
- 4.00 - 5.35 (9H, multiplet);
- 7.10 - 8.30 (7H, multiplet).

30 PREPARATION 32

4-Nitrobenzyl (1R,5R,6S)-2-(diphenylphosphoryloxy)-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate

35 3.63 g of 4-nitrobenzyl (1R,5R,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-oxo-1-carbapenam-3-carboxylate were dissolved in 72 ml of dry acetonitrile, and then 2.28 ml of diphenylphosphoric acid chloride and 1.92 ml of diisopropylethylamine were added dropwise to the resulting solution, whilst stirring and ice-cooling. The resulting mixture was then stirred for a further 1 hour under the same conditions, after which it was concentrated by evaporation under reduced pressure. The resulting residue was dissolved in ethyl acetate and washed twice with water and then with an aqueous solution of sodium chloride, after which it was dried over anhydrous sodium sulphate and again concentrated by evaporation under reduced pressure. The residue was dissolved in 10 ml of ethyl acetate, and the resulting solution was left to stand to precipitate crystals. The mixture was diluted with 500 ml of diisopropyl ether, and crystals formed were collected by filtration and dried to obtain 5.34 g of the title compound, as colourless needle-like crystals, melting at 123 - 125°C.

40 Nuclear Magnetic Resonance Spectrum (270MHz, CDCl₃) δ ppm:

- 45 1.22 (3H, doublet, J = 7.2 Hz);
- 1.33 (3H, doublet, J = 6.6 Hz);
- 3.32 (1H, doublet of doublets, J = 6.6 & 2.6 Hz);
- 3.42 - 3.56 (1H, multiplet);
- 4.20 - 4.31 (2H, multiplet);
- 5.22 (1H, doublet, J = 13.8 Hz);
- 5.35 (1H, doublet, J = 13.8 Hz);
- 7.13 - 7.40 (10H, multiplet);
- 7.55 (1H, doublet, J = 8.6 Hz);
- 8.13 (2H, doublet, J = 8.6 Hz).

PREPARATION 33(2S,4S)-4-Mercapto-2-[1-(4-nitrobenzyloxycarbonyl)aztidin-3-ylaminocarbonyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine

5

Following a procedure similar to that described in Preparation 22, the title compound was prepared.
 Infrared Absorption Spectrum (liquid film), ν_{max} cm⁻¹:

1709, 1662, 1609, 1523, 1435, 1406, 1348, 1287.

Nuclear Magnetic Resonance Spectrum (270MHz, hexadeuterated dimethyl sulphoxide + D₂O) δ ppm:

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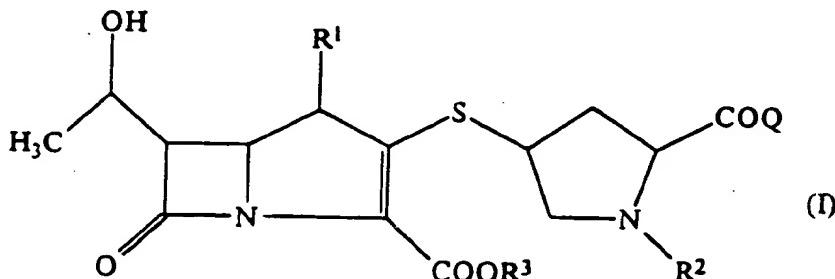
1.86 - 2.04 (1H, multiplet);
 2.65 - 2.80 (1H, multiplet);
 2.98 - 3.61 (5H, multiplet);
 3.87 - 4.53 (4H, multiplet);
 5.08 - 5.27 (4H, multiplet);
 15 7.51 - 7.67 (4H, multiplet);
 8.14 - 8.26 (4H, multiplet).

Claims

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1. Compounds of formula (I) and pharmaceutically acceptable salts and esters thereof:

25



30

in which:

35

R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, an alkynyl group having from 2 to 6 carbon atoms, or, provided that Q does not contain a quaternary nitrogen atom, a group of formula -C(=NH)R⁰,

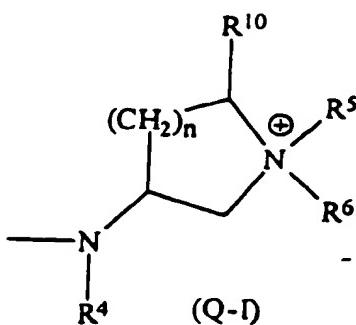
where R⁰ represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms;

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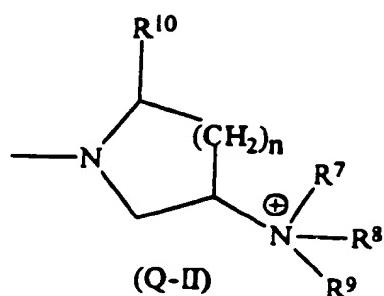
R³ represents a hydrogen atom, a negative ion or a carboxy-protecting group; and

Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-IV), (Q-V), (Q-VI), (Q-VII), (Q-VIII), (Q-IX), (Q-X), (Q-XI), (Q-XII) and (Q-XIII):

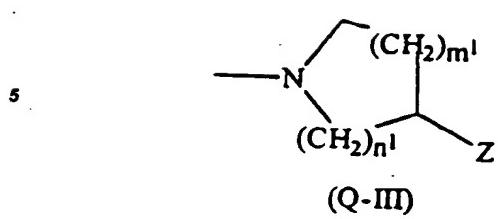
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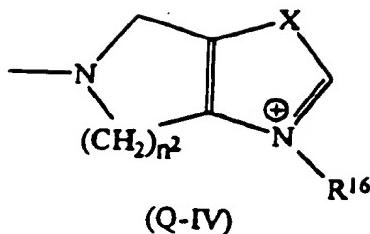
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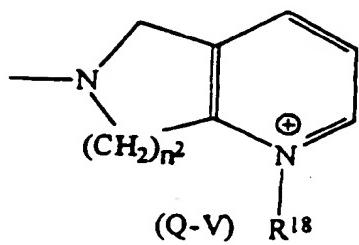
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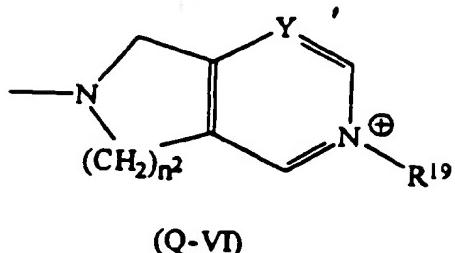
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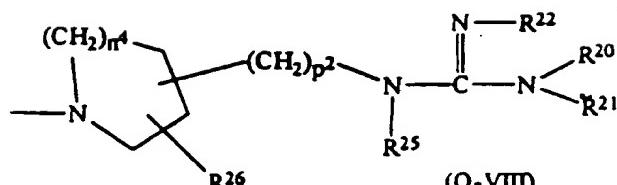
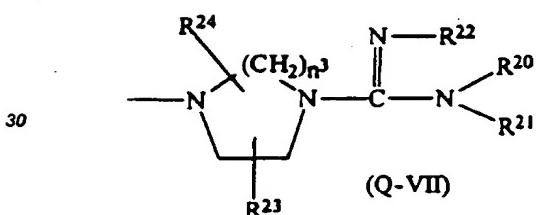
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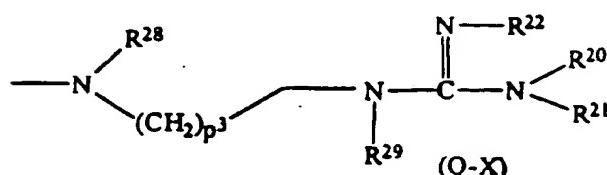
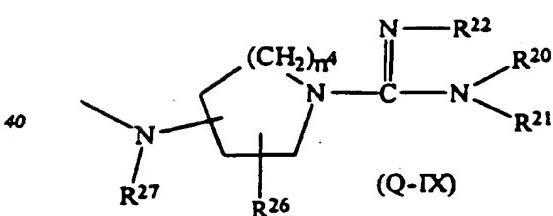
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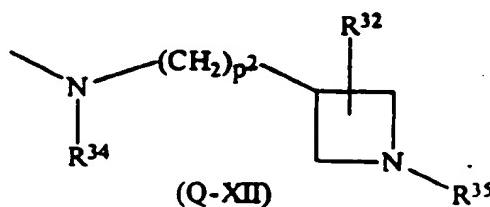
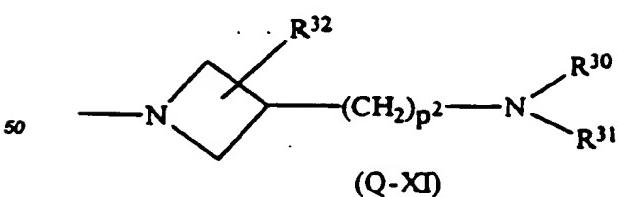
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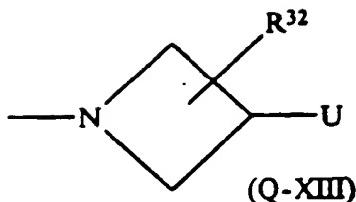


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in which:

R⁴ represents a hydrogen atom or a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

15

R⁵ and R⁶ are the same or different and each represents a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

or

R⁴ and R⁵ together represent a group of formula -(CH₂)_m- where m is 2 or 3;

20

R⁷, R⁸ and R⁹ are the same or different and each represents a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

25

R¹⁰ represents a hydrogen atom, a carbamoyl group, or a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

or

R⁷ and R⁸ together represent a group of formula -(CH₂)_p-(W)_w-(CH₂)_q-, where p is 0, 1, 2 or 3, q is 0, 1, 2 or 3, W represents an oxygen or sulfur atom and w is 0 or 1, provided that (p + q + w) is an integer from 2 to 6;

or

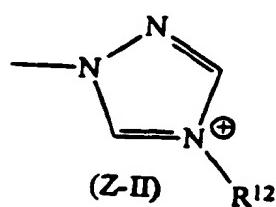
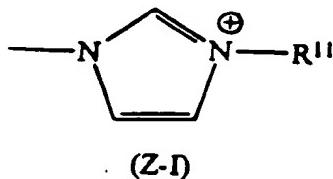
R⁷ and R¹⁰ together represent a group of formula -(CH₂)_{p'}-(W)_{w'}-(CH₂)_{q'}-, where p' is 0, 1, 2 or 3, q' is 0, 1, 2 or 3, W represents an oxygen or sulfur atom and w' is 0 or 1 provided that (p' + q' + w') is at least one;

30

n is 0 or 1;

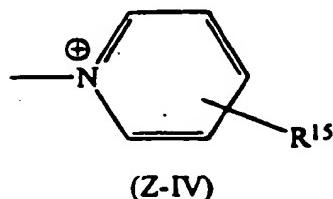
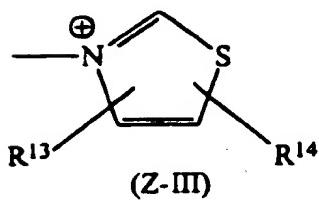
Z represents a group of formula (Z-I), (Z-II), (Z-III), (Z-IV), (Z-V), (Z-VI), (Z-VII) or (Z-VIII):

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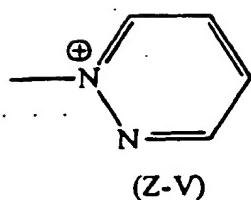
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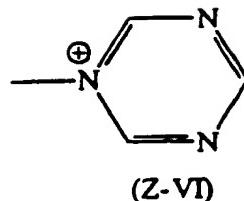
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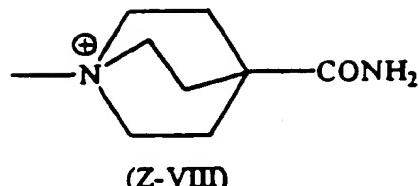
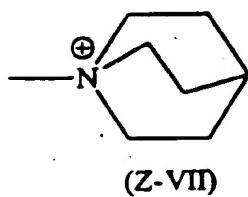


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in which:

R¹¹ and R¹² are the same or different and each represents a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms; and

R¹³, R¹⁴ and R¹⁵ are the same or different and each represents a carbamoyl group, or a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

30

m¹ is 0 or 1 and n¹ is 0, 1 or 2, provided that (m¹ + n¹) is greater than 0;

R¹⁶ represents a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

R¹⁸ represents a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

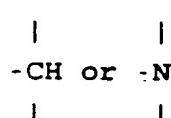
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X represents a sulfur atom or a group of formula >NR¹⁷, where R¹⁷ represents an unsubstituted alkyl group having from 1 to 6 carbon atoms or a substituted alkyl group which has from 1 to 6 carbon atoms and which is substituted by a single substituent selected from halogen atoms, carbamoyl groups and hydroxy groups; n² is 1 or 2;

R¹⁹ represents a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

Y represents a group of formula

40



45

R²⁰, R²¹ and R²² are the same or different and each represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 6 carbon atoms;

or

R²⁰ and R²¹ or R²⁰ and R²² together represent a group of formula -(CH₂)_s-(W)-CH₂_t, where s is 0, 1, 2 or 3, t is 0, 1, 2 or 3, W represents an oxygen or sulfur atom and w' is 0 or 1;

R²³ and R²⁴ are the same or different and each represents a hydrogen atom, a halogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, a hydroxy group, a carboxy group, a carbamoyl group, an amin group, a cyan group or a carbamoyloxy group;

n³ is 1, 2 or 3;

55

R²⁵ represents a hydrogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, or an alkynyl group having from 2 to 6 carbon atoms;

R²⁶ represents a hydrogen atom, a halogen atom, a substituted or unsubstituted alkyl group having from

1 to 6 carbon atoms, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group or a carbamoyloxy group;

n⁴ is 0, 1 or 2;

p² is 0 or 1;

5 R²⁷ represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 6 carbon atoms; R²⁸ and R²⁹ are the same or different and each represents a hydrogen atom or a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms;

p³ is 1 or 2;

10 R³⁰ represents a hydrogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, an alkynyl group having from 2 to 6 carbon atoms, or a group of formula -C(=NH)R³³,

where R³³ represents a hydrogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, a cycloalkyl group having from 3 to 6 ring carbon atoms or a cycloalkylalkyl group in which the cycloalkyl part has from 3 to 6 ring carbon atoms and the alkyl part has from 1 to 6 carbon atoms;

15 R³¹ represents a hydrogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, or an alkynyl group having from 2 to 6 carbon atoms;

R³² represents a hydrogen atom, a halogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group 20 or a carbamoyloxy group;

R³⁴ represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 6 carbon atoms;

R³⁶ represents a hydrogen atom, a substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 6 carbon atoms, an alkynyl group having from 2 to 6 carbon atoms, or a group of formula -C(=NH)R³³, where R³³ is as defined above; and

25 U represents an imidazolyl group, a triazolyl group or a tetrazolyl group.

2. A compound according to Claim 1, in which:

R¹ represents a hydrogen atom or a methyl group;

30 R² represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents A¹, defined below, an alkenyl group having 3 or 4 carbon atoms, an alkynyl group having 3 or 4 carbon atoms, or, provided that Q does not contain a quaternary nitrogen atom, a group of formula -C(=NH)R⁰, where R⁰ represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms;

R³ represents a hydrogen atom or a negative ion; and

35 Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-IV), (Q-V), (Q-VI), (Q-VII), (Q-VIII), (Q-IX), (Q-X), (Q-XI), (Q-XII) and (Q-XIII), defined in Claim 1, in which:

R⁴ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

40 R⁵ and R⁶ are the same or different and each represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

or

R⁴ and R⁵ together represent a group of formula -(CH₂)_m-, where m is 2 or 3;

45 R⁷, R⁸ and R⁹ are the same or different and each represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

R¹⁰ represents a hydrogen atom, a carbamoyl group, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by 50 at least one of substituents B¹, defined below;

or

R⁷ and R⁸ together represent a group of formula -(CH₂)_p-(W)_w-(CH₂)_q-, where p is 0, 1, 2 or 3, q is 0, 1, 2 or 3, W represents an oxygen or sulfur atom and w is 0 or 1, provided that (p + q + w) is an integer from 2 to 6;

55 R⁷ and R¹⁰ together represent a group of formula -(CH₂)_{p'}-(W)_{w'}-(CH₂)_{q'}-, where p' is 0, 1, 2 or 3, q' is 0, 1, 2 or 3, W represents an oxygen or sulfur atom and w' is 0 or 1;

n is 0 or 1;

Z represents a group of formula (Z-I), (Z-II), (Z-III), (Z-IV), (Z-V), (Z-VI), (Z-VII) or (Z-VIII), defined in Claim 1, in which:

5 R¹¹ and R¹² are the same or different and each represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below; and

R¹³, R¹⁴ and R¹⁵ are the same or different and each represents a carbamoyl group, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

m¹ is 0 or 1 and n¹ is 0, 1 or 2, provided that (m¹ + n¹) is greater than 0;

10 R¹⁶ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

R¹⁸ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B¹, defined below;

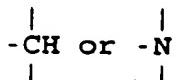
15 X represents a sulfur atom or a group of formula >NR¹⁷, where R¹⁷ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one substituent selected from carbamoyl groups and hydroxy groups;

n² is 1 or 2;

20 R¹⁹ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one carbamoyl and/or hydroxy-substituent;

Y represents a group of formula

25



30 R²⁰, R²¹ and R²² are the same or different and each represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

or

R²⁰ and R²¹ or R²⁰ and R²² together represent a group of formula -(CH₂)_s-(W)_w-(CH₂)_t, where s is 1 or 2, t is 1 or 2, W represents an oxygen or sulfur atom and w is 0 or 1, provided that (s + w + t) is 2, 3 or 4;

35 R²³ and R²⁴ are the same or different and each represents a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents C¹ defined below, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group or a carbamoyloxy group;

n³ is 1, 2 or 3;

40 R²⁵ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents C¹, defined below, an alkenyl group having 3 or 4 carbon atoms, or an alkynyl group having 3 or 4 carbon atoms;

45 R²⁶ represents a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents C¹, defined below, a hydroxy group, a carboxy group, a carbamoyl group, an amino group, a cyano group or a carbamoyloxy group;

n⁴ is 0, 1 or 2;

p² is 0 or 1;

50 R²⁷ represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

R²⁸ and R²⁹ are the same or different and each represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents C¹, defined below;

p³ is 1 or 2;

55 R³⁰ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents D¹, defined below, an alkenyl group having 3 or 4 carbon atoms, an alkynyl group having 3 or 4 carbon atoms, or a group of formula -C(=NH)R³¹,

where R³³ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one substituent selected from halogen atoms and alkoxy groups having from 1 to 3 carbon atoms, a cycloalkyl group having from 3 to 6 ring carbon atoms or a cycloalkylalkyl group in which the cycloalkyl part has from 3 to 6 ring carbon atoms and the alkyl part has 1 or 2 carbon atoms;

R³¹ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents F¹, defined below, an alkenyl group having 3 or 4 carbon atoms, or an alkynyl group having 3 or 4 carbon atoms;

R³² represents a hydrogen atom, a halogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

R³⁴ represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

R³⁵ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents G¹, defined below, an alkenyl group having 3 or 4 carbon atoms, an alkynyl group having 3 or 4 carbon atoms, or a group of formula -C(=NH)R³³, where R³³ is as defined above; and

U represents an imidazolyl group, a triazolyl group or a tetrazolyl group;

substituents A¹ are selected from hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups, halogen atoms and amino groups;

substituents B¹ are selected from cyano groups, hydroxy groups, carboxy groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms, alkylthio groups having from 1 to 3 carbon atoms, alkylsulfinyl groups having from 1 to 3 carbon atoms, alkylsulfonyl groups having from 1 to 3 carbon atoms, alkanoylamino groups having from 1 to 5 carbon atoms, alkanoyloxy groups having from 1 to 5 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, alkoxy carbonyl groups having from 2 to 5 carbon atoms, ureido groups, carbamoyl groups, alkylcarbamoyl groups having from 2 to 5 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 3 carbon atoms, carbamoyloxy groups, alkylcarbamoyloxy groups having from 2 to 5 carbon atoms, dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 4 carbon atoms, amino groups, alkylamino groups having from 1 to 4 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 4 carbon atoms, oxygen atoms and cycloalkyl groups having from 3 to 6 ring carbon atoms;

substituents C¹ are selected from hydroxy groups, carboxy groups, carbamoyl groups, halogen atoms and amino groups;

substituents D¹ are selected from hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, cyano groups, ureido groups, alkoxy groups having from 1 to 3 carbon atoms, alkoxy carbonyl groups having from 2 to 5 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, alkanoylamino groups having from 1 to 5 carbon atoms, alkanoyloxy groups having from 1 to 5 carbon atoms, halogen atoms, amino groups, alkylamino groups having from 1 to 3 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 3 carbon atoms, alkylcarbamoyl groups having from 2 to 5 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 3 carbon atoms, alkylcarbamoyloxy groups having from 2 to 5 carbon atoms and dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 3 carbon atoms;

substituents F¹ are selected from hydroxy groups, carboxy groups, carbamoyl groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms and amino groups; and

substituents G¹ are selected from hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms and amino groups.

3. A compound according to Claim 1, in which:

R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents A², defined below, or, provided that Q does not contain a quaternary nitrogen atom, a group of formula -C(=NH)R⁶,

where R⁶ represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms;

R³ represents a hydrogen atom or a negative ion; and

Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-IV), (Q-V), (Q-VI), (Q-VII), (Q-VIII), (Q-IX), (Q-X), (Q-XI), (Q-XII) and (Q-XIII), defined in Claim 1, in which:

R⁴ represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of sub-

stituents B², defined below;

R^5 and R^6 are the same or different and each represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B^2 , defined below:

5 **or**

R⁴ and R⁵ together represent a group of formula -(CH₂)_m-, where m is 2 or 3:

R⁷, R⁸ and R⁹ are the same or different and each represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B², defined below:

R¹⁰ represents a hydrogen atom, a carbamoyl group, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one substituent selected from hydroxy groups, amino groups and halogen atoms;

or

15 R⁷ and R⁸ together represent a group of formula -(CH₂)_p-(W)_w-(CH₂)_q-, where p is 1 or 2, q is 1, 2 or 3, W represents an oxygen or sulfur atom and w is 0 or 1, provided that (p + q + w) is an integer from 4 to 6;

or

R⁷ and R¹⁰ together represent a group of formula -(CH₂)_p- where p' is 1, 2 or 3; n is 0 or 1;

Z represe

R₁₁ and **R₁₂** are the same or different and each represents an univalent and soluble organic residue.

R^+ and R^- are the same or different and each represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B^2 , defined below; and

25 R₁₃, R₁₄ and R₁₅ are the same or different and each represents a carbamoyl group, an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B², defined below:

M¹ is 0 or 1 and **n¹** is 0, 1 or 2, provided that (**m¹** + **n¹**) is an integer from 1 to 3;

R^{16} represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B^2 , defined below;

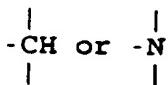
R¹⁸ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms, or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents B², defined below;

X represents a sulfur atom or a group of formula $>NR^{17}$, where R¹⁷ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one substituent selected from carbamoyl groups and hydroxy groups;

n² is 1 or 2;
R¹⁹ represents an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one substituent selected from

carbamoyl groups and hydroxy groups;
Y represents a group of formula

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R²⁰, R²¹ and R²² are the same or different and each represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;

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R^{ω} and R^{x1} or R^{x2} and R^{z2} together represent a group of formula $-(CH_2)_s-W-(CH_2)_t-$, where s is 1 or 2, t is 1 or 2, W represents an oxygen or sulfur atom and w' is 0 or 1, provided that $(s + w' + t)$ is 2, 3 or 4; R^{z1} and R^{z2} together represent a group of formula $-(CH_2)_w-$, where w is 1 or 2.

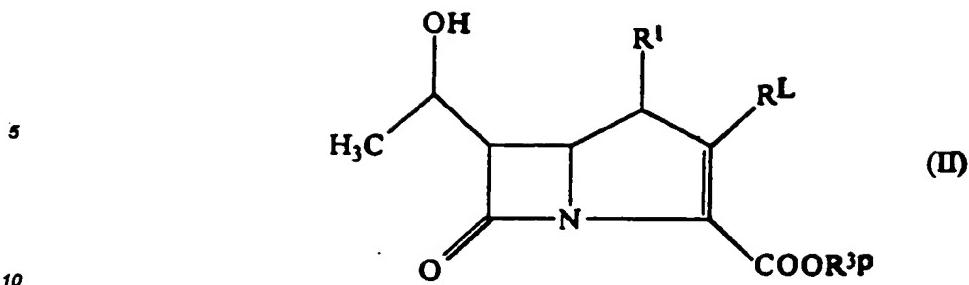
R^{23} and R^{24} are the same or different and each represents a hydrogen atom, a halogen atom, a hydroxy group, a carbamoyl group, a carboxy group, an unsubstituted alkyl group having from 1 to 3 carbon atoms or a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one substituent selected from hydroxy groups, amino groups and carbamoyl groups;

0^3 is 1, 2 or 3.

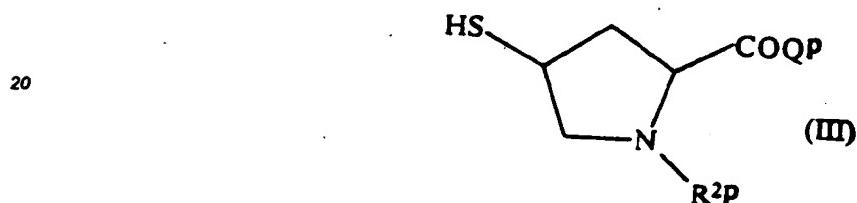
R^{25} represents a hydrogen atom or a methyl group:

- R^{28} represents a hydrogen atom;
 n^4 is 0, 1 or 2;
 p^2 is 0 or 1;
- R^{27} represents a hydrogen atom or a methyl group;
- 5 R^{28} and R^{29} are the same or different and each represents a hydrogen atom or a methyl group;
 p^3 is 1 or 2;
- 10 R^{30} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents D^2 , defined below, an alkenyl group having 3 carbon atoms, an alkynyl group having 3 carbon atoms, or a group of formula $-C(=NH)R^{33}$,
- where R^{33} represents a hydrogen atom, a methyl group, a substituted alkyl group which has 1 or 2 carbon atoms and which is substituted by at least one halogen and/or methoxy substituent, a cyclopropyl group or a cyclopropylmethyl group;
- 15 R^{31} represents a hydrogen atom or an unsubstituted alkyl group having from 1 to 3 carbon atoms;
- R^{32} represents a hydrogen atom;
- 16 R^{34} represents a hydrogen atom or a methyl group;
- 17 R^{35} represents a hydrogen atom, an unsubstituted alkyl group having from 1 to 3 carbon atoms, a substituted alkyl group which has from 1 to 3 carbon atoms and which is substituted by at least one of substituents G^2 , defined below, or a group of formula $-C(=NH)R^{33}$, where R^{33} is as defined above; and
- 20 U represents an imidazolyl group, a triazolyl group or a tetrazolyl group;
- substituents A^2 are selected from hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms and amino groups;
- 25 substituents B^2 are selected from cyano groups, hydroxy groups, carboxy groups, halogen atoms, alkoxy groups having from 1 to 3 carbon atoms, alkanoylamino groups having from 1 to 5 carbon atoms, alkanoyloxy groups having from 1 to 5 carbon atoms, alkanoyl groups having from 1 to 5 carbon atoms, alkoxycarbonyl groups having from 2 to 5 carbon atoms, ureido groups, carbamoyl groups, alkylcarbamoyl groups having from 2 to 5 carbon atoms, dialkylcarbamoyl groups in which each alkyl part has from 1 to 3 carbon atoms, carbamoyloxy groups, alkylcarbamoyloxy groups having from 2 to 5 carbon atoms, dialkylcarbamoyloxy groups in which each alkyl part has from 1 to 4 carbon atoms, amino groups, alkylamino groups having from 1 to 4 carbon atoms, dialkylamino groups in which each alkyl part has from 1 to 4 carbon atoms and cycloalkyl groups having from 3 to 6 ring carbon atoms;
- 30 substituents D^2 are selected from hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms, amino groups, alkylamino groups having from 1 to 3 carbon atoms and dialkylamino groups in which each alkyl part has from 1 to 3 carbon atoms;
- 35 substituents G^2 are selected from hydroxy groups, carboxy groups, carbamoyl groups, carbamoyloxy groups, halogen atoms, methoxy groups and amino groups.
4. A compound according to Claim 1, in which Q represents a group of formula (Q-I), (Q-II), (Q-III), (Q-VII), (Q-VIII) or (Q-XI).
- 40 5. A compound according to Claim 1, in which Q represents a group of formula (Q-II), (Q-III), (Q-VII) or (Q-XI).
6. A compound according to Claim 1, in which R^1 represents a methyl group.
- 45 7. A compound according to Claim 1, in which Q represents a group of formula (Q-II), (Q-III), (Q-VII) or (Q-XI), and R^1 represents a methyl group.
8. A compound according to Claim 2, in which Q represents a group of formula (Q-II), (Q-III), (Q-VII) or (Q-XI), and R^1 represents a methyl group.
- 50 9. A compound according to Claim 3, in which Q represents a group of formula (Q-II), (Q-III), (Q-VII) or (Q-XI), and R^1 represents a methyl group.
- 55 10. 6-(1-Hydroxyethyl)-1-methyl-2-[2-(3-trimethylammoniopyrrolidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-1-carbapen-2-em-3-carboxylate and pharmaceutically acceptable salts thereof.
11. 2-(2-[3-(Carbamoylmethyldimethylammonio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio)-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate and pharmaceutically acceptable salts thereof.

12. 2-[2-{3-[(2-Hydroxyethyl)dimethylammonio]pyrrolidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate and pharmaceutically acceptable salts thereof.
- 5 13. 2-[2-{3-[N-(2-Fluoroethyl)-N,N-dimethylammonio]pyrrolidin-1-ylcarbonyl}pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylate and pharmaceutically acceptable salts thereof.
- 10 14. 6-(1-Hydroxyethyl)-1-methyl-2-{2-[3-(3-methylimidazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio}-1-carbapen-2-em-3-carboxylate and pharmaceutically acceptable salts thereof.
- 15 15. 2-[2-(4-Amidinopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 20 16. 2-[2-(4-Amidinopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 25 17. 2-[2-(4-Amidinohomopiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 30 18. 2-[2-(4-Amidinohomopiperazin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 35 19. 2-[2-(3-Aminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 40 20. 2-[2-(3-Acetimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 45 21. 2-[2-(3-Formimidoylaminoazetidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 50 22. 2-[2-(3-Aminoazetidin-1-ylcarbonyl)-1-methylpyrrolidin-4-ylthio]-6-(1-hydroxyethyl)-1-methyl-1-carbapen-2-em-3-carboxylic acid and pharmaceutically acceptable salts thereof.
- 55 23. 6-(1-Hydroxyethyl)-1-methyl-2-{2-[3-(4-methyl-1,2,4-triazolio)pyrrolidin-1-ylcarbonyl]pyrrolidin-4-ylthio}-1-carbapen-2-em-3-carboxylate and pharmaceutically acceptable salts thereof.
28. The use of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, as claimed in any one of Claims 1 to 26, as a pharmaceutical.
29. The use of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, as claimed in any one of Claims 1 to 26, for the manufacture of a medicament for the treatment or prevention of microbial infections.
30. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, as claimed in any one of Claims 1 to 26, which comprises the steps: reacting a carbapenem compound of formula (II):



(in which R¹ is as defined in Claim 1, R^L represents a sulfonyloxy or phosphoryloxy group or a group of formula -S(O)R^{L1}, R^{L1} represents an alkyl group, a haloalkyl group, an alkanoylaminoalkyl group, an alkenoylaminoalkyl group, an aryl group or an aromatic heterocyclic group, and R^{3P} represents a carboxy-protecting group) with a pyrrolidine derivative of formula (III):



(in which R^{2P} represents any of the groups or atoms represented by R² or any such group or atom which has been protected, and Q^P represents any of the groups or atoms represented by Q or any such group or atom which has been protected or any such group in which a quaternary nitrogen atom is replaced by a corresponding tertiary nitrogen atom, and, where the group Q^P contains a quaternary nitrogen atom, the compound is accompanied by a balancing anion),
 and, if necessary, converting any non-quaternized nitrogen atom to the corresponding quaternary nitrogen in the group of formula (Q-I), (Q-II), (Q-IV), (Q-V) or (Q-VI) or in the group represented by Z,
 and, if necessary, removing any protecting groups,
 and optionally silylating and/or esterifying the product.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 30 1872

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. CL.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X, P, D	EP-A-0 518 558 (SANKYO COMPANY LTD.) * examples 1-47; 4-1; table 7. Line 55, page 6 *	1, 27-29	C07D477/00 A61K31/40
Y, D	EP-A-0 126 587 (SUMITOMO CHEMICAL COMPANY) * examples 3, 4, 5, 29, 14, 15, 32, 35, 36, 41 *	1, 27-29	
Y	EP-A-0 243 686 (SUMITOMO PHARMACEUTICALS COMPANY LTD.) * examples 7-14 *	1, 27-29	
Y, D	EP-A-0 442 497 (SUMITOMO PHAMACEUTICALS COMPANY LTD.) * compounds 2-4, 12, 17, 18, 74 *	1	
Y, D	EP-A-0 443 883 (SANKYO COMPANY LTD) * the whole document *	1, 27-29	
-----			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07D A61K
The present search report has been drawn up for all claims			
Place of search BERLIN	Date of completion of the search 22 JUNE 1993	Examiner FRELON D. L. M. F.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			